VOLUME 60 *December 1949* NUMBER 6

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

The Surgical Treatment of Recurrent and Chronic Spontaneous Pneumothorax of Nontuberculous Origin. Richard H. Meade, Jr., and Brian B. Blades 683
The Surgical Importance of the Anatomical Distribution of the Pulmonary Segments. Edward M. Kent 699
The Physiological Effects of Pneumoperitoneum upon the Respiratory Apparatus. George W. Wright, Ronald Place, and Frank Prinzi 706
Evaluation of Streptomycin Regimens in the Treatment of Tuberculosis. An Account of the Study of the Veterans Administration, Army, and Navy, July 1946 to April 1949. William B. Tucker 715
Diffuse Pulmonary Granulomatosis in Young Women following Exposure to Beryllium Compounds in the Manufacture of Radio Tubes. Report of Five Cases. Paul Slavin 755
Tuberculosis among Selective Service Registrants. Mapheus Smith, Lester T. Reynolds, and M. Ethel Hand 773

Case Reports:
Pulmonary Alveolar Adenomatosis. Sidney J. Shipman, H. Brodie Stephens, and Frederick M. Binkley 788
Fatal Tension Pneumothorax Resulting from Diaphragmatic Rupture in a Patient Receiving Pneumoperitoneum. S. A. Yannitelli, C. E. Woodruff, E. E. Mueller, and W. L. Howard 794
Tuberculous Arteritis of the Abdominal Aorta with Rupture into the Third Portion of the Duodenum. Report of a Case. Harold Zarowitz and David M. Grayzel 801

Letters to the Editors:
Chemotherapeutic Action of Streptomycin Para-aminosalicylate in Experimental Tuberculosis in Mice. Gladys L. Hobby, Peter P. Regna, and Tulita F. Lenert 808
The Effect of Antihistamine Medication on the Tuberculin Reaction. Alfred R. Henderson 811
Obituary: Bruce H. Douglas, 1892–1949 812
Books 815
Index of Subjects and Authors 819
Index of Abstracts 81

ANNUAL MEETING—WASHINGTON, D.C.
April 25–28, 1950

See page 8

Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N. Y.

Copyright 1949, by the National Tuberculosis Association

PRINTED IN U. S. A.

THE AMERICAN REVIEW
OF
TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY

EDITOR-IN-CHIEF
ESMOND R. LONG
Philadelphia Pa.

MANAGING EDITOR
WALSH McDERMOTT
New York, N. Y.

EDITORIAL BOARD

W. EDWARD CHAMBERLAIN, Philadelphia, Pa.
HALBERT L. DUNN, Washington, D.C.
H. CORWIN HINSHAW, San Francisco, Calif.
KIRBY S. HOWLETT, JR., Shelton, Conn.
JOHN C. JONES, Los Angeles, Calif.
ALEXANDER D. LANGMUIR, Baltimore, Md.
HERBERT C. MAIER, New York, N. Y.
WILLIAM P. SHEPARD, San Francisco, Calif.
C. EUGENE WOODRUFF, Northville, Mich.

NOTICE TO SUBSCRIBERS AND CONTRIBUTORS

THE AMERICAN REVIEW OF TUBERCULOSIS is published by the National Tuberculosis Association and issued monthly about the 1st of the month. THE AMERICAN REVIEW OF TUBERCULOSIS is the Official Journal of the American Trudeau Society. A volume includes six numbers and begins with the January and July numbers.

Subscriptions: The subscription price of the REVIEW is $8.00 for the calendar year. Checks should be made payable to Collier Platt, Treasurer.

Character of the Review: The REVIEW consists of two main parts, namely, (1) original articles and (2) abstracts. The original part is published monthly, its size depending upon the amount of manuscript in hand. Abstracts will appear as the amount of material warrants. Each part will be paged separately, to permit permanent separate binding upon the completion of a volume.

Manuscripts: The REVIEW invites the submission of manuscripts on any phase of tuberculosis, nontuberculous pulmonary diseases, and related subjects of interest. Illustrations for reproduction must be of first class quality. It is essential that photographs and reproductions of roentgenograms clearly furnish all the detail the author wishes illustrated. Articles are accepted for publication with the understanding that they are contributed solely to THE AMERICAN REVIEW OF TUBERCULOSIS.

Manuscripts should be sent to the office of the Managing Editor, Dr. Walsh McDermott, 1790 Broadway, New York 19, N. Y. They should be in English, typewritten on one side of the page only and with wide spacing and margins. In order to hasten the process of reviewing and editing, it is requested that each original manuscript be accompanied by a duplicate copy. This will be returned to the author when a final decision regarding publication is made. The manuscripts should be mailed flat and transmitted by first-class mail with postage for return if not available. Authors should exercise particular care in the preparation, notation and description of figures, charts and tables.

The publishers will not be responsible for manuscripts, illustrations, etc., lost in transit. In order to save expense for authors' corrections in proof, manuscript should be carefully revised by the author before submission.

Abstracts: Authors wishing to have abstracts of their papers appear in ABSTRACTS OF TUBERCULOSIS will facilitate their publication by sending concise abstracts or reprints to the Managing Editor.

Reprints: Fifty reprints without covers of articles will be furnished to authors free of charge when requested in advance. A table showing cost of additional reprints, with an order blank is submitted with proofs to the authors.

Single Copies: The price of single copies of this number of THE AMERICAN REVIEW OF TUBERCULOSIS is one dollar postpaid.

Advertising: Rates will be furnished by THE AMERICAN REVIEW OF TUBERCULOSIS, 1790 Broadway, New York 19, N. Y. on request.

The Publishers reserve the right to decline any advertising submitted and to censor all copy. **Acceptance of an advertisement does not constitute official endorsement of the product advertised.**

Entered as second-class matter March 9, 1917, at the post office at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at special rate of postage provided for in section 1103, act of October 3, 1917. Authorized on July 2, 1918.

new
common cold therapy
. . . without drowsiness

Early treatment with Thephorin-AC tablets will frequently abort or relieve the common cold with little likelihood of drowsiness. Thephorin-AC is therefore of particular value to motorists, machine operators and ambulatory patients who must remain alert. It combines the antihistaminic effect of Thephorin with the action of acetophenetidin, acetylsalicylic acid and caffeine. In over 2,000 attacks of the common cold, Brewster* found that Thephorin "is effective . . . and will abort a high percentage of the attacks."

HOFFMANN-LA ROCHE INC • NUTLEY 10 • N. J.

Thephorin®-AC
tablets

'Roche'

*J. M. Brewster, *In Press.*
(*Thephorin—brand of phenindamine*)

Zavod ANEROID PNEUMO Apparatus

THIS is a simplified apparatus for pneumothorax or other procedures requiring the introduction of measured amounts of air into the body cavities under manometric control. It consists essentially of a glass cylinder with an accurately fitted piston. By means of a hand operated cautery bulb, constant pressure is exerted on one face of the piston causing it to move and deliver air ahead of it. The movement of the piston and delivery of air can be stopped instantly by manipulation of the valve. Less than 5 cc of air can be accurately administered, as well as any desired larger amount. Therefore, the capacity of the apparatus is unlimited as it is not dependent upon the volume of a flask.

One complete excursion of the piston delivers 150 cc of air. Turning the valve immediately starts the piston in the other direction, continuing to supply air without any change of connections. Air can be delivered either slowly or rapidly as desired. An aneroid manometer is in the circuit at all times, indicating air pressure during instillation as well as the pressure in the chest when the valve is turned to zero.

Descriptive Literature and Reprints are Available

AMERICAN CYSTOSCOPE MAKERS, INC.
FREDERICK J. WALLACE, PRESIDENT
1241 LAFAYETTE AVENUE NEW YORK 59, N.Y.

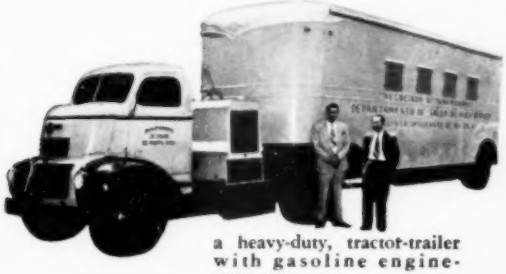
for Your case-finding program

wherever it is...
however the conditions...
whatever the budget...

a small car-drawn carriet for transporting Minograph to survey site

a self-contained x-ray clinic in a special bus body

a completely equipped bus, with darkroom and office provisions



a heavy-duty, tractor-trailer with gasoline engine-generator

a light truck to carry Minograph components for quick assembly on location

there's a "Minograph" mobile x-ray screening unit to fit...exactly

A Picker representative can save weeks of data-digging for any TB specialist or group interested in case-finding. There are Picker offices in principal cities of U.S.A. and Canada ... or write us

PICKER X-RAY CORPORATION
300 Fourth Ave., New York 10, N. Y.

Picker x-ray

Meat...

Outstanding Value . . .

Outstanding Nutritional Benefits

Whether the pocketbook calls for economy or permits satisfaction of that urge for the fanciest cuts, meat gives your patients full value for their money. Every cut and kind of meat supplies, *in abundance*, these essential nutrients:

1. Biologically complete protein . . . the kind which satisfies the requirements for growth and which is needed daily for tissue maintenance, antibody formation, hemoglobin synthesis, and good physical condition.
2. The essential B complex vitamins, thiamine, riboflavin, and niacin.
3. Essential minerals, including iron in particular.

In addition to these tangible values, meat ranks exceptionally high not only in taste and palate appeal, but also in satiety value.

The instinctive choice of meat as man's favorite protein food has behind it sound nutritional justification.*

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

*McLester, J. S.: Protein Comes Into Its Own, J.A.M.A. *139*:897 (Apr. 2,) 1949

American Meat Institute

Main Office, Chicago...Members Throughout the United States

LATEST VITAMIN FACTS

From Merck—where many of the vitamin factors were first synthesized.

These six Merck *Vitamin Reviews* are yours for the asking while the editions last. These concise reviews contain up-to-date, authoritative facts and can be most useful for quick reference. Please address requests for copies to Merck & Co., Inc., Rahway, N. J.

PARTIAL INDEX OF CONTENTS

- **Factors that produce avitaminosis.**
- **Signs and symptoms of deficiency.**
- **Daily requirements and dosages.**
- **Distribution in foods.**
- **Methods of administration.**
- **Clinical use in specific conditions.**

MERCK VITAMINS

MERCK & CO., Inc. *Manufacturing Chemists* RAHWAY, N. J.

	Calories	Protein Gm.	Calcium Gm.	Copper mg.	Iron mg.	Phosphorus Gm.	Vitamin A I. U.	Thiamine mg.	Riboflavin mg.	Niacin mg.	Ascorbic Acid mg.	Vitamin D I. U.
National Research Council Allowances. Sedentary Man (154 lbs.)	2,400	70	1.0	1.2	12	1.5	5,000	1.2	1.8	12	75	Small Amount
Ovaltine in Milk, 3 Servings *	676	32	1.12	0.5	12	0.94	3,000	1.16	2.0	6.8	30	417
Percentages of N. R. C. Allowances Provided by 3 Servings* of Ovaltine in Milk	28%	46%	112%	42%	100%	63%	60%	97%	111%	57%	40%	Abundance

*Each serving made of ⅓ oz. of Ovaltine and 8 fl. oz. of whole milk.

In Protecting Dietary Adequacy

of the tuberculous patient

The *multiple nutrient dietary food supplement*, Ovaltine in milk, is highly qualified for protecting the nutrient adequacy of the diet of the tuberculous patient. This is strikingly obvious from the data in the above table listing:

(1) The National Research Council's Recommended Daily Dietary Allowances (revised 1948) for a sedentary man of 154 lbs.,

(2) The nutrient content of three servings of Ovaltine in milk, and

(3) The percentages of the Council's Dietary Allowances provided by the three servings of Ovaltine in milk.

Enticing flavor and easy digestibility are other features of Ovaltine in milk important to the tuberculous patient. During periods of food resistance, which may constitute a severe threat to the nutritional state, this delicious dietary supplement is particularly valuable.

Two kinds, Plain and Sweet Chocolate Flavored. Serving for serving, they are virtually identical.

Ovaltine

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

PULMONARY TUBERCULOSIS

Dr. Hans Jacob Ustevdt brilliantly discusses modern ideas concerning the psychology and treatment of tuberculosis. His close work with Scheel and Heimbock of Oslo, their epoch-making work and notable advances in tuberculosis studies make this book valuable for General Practitioners, students and tuberculosis specialists. Generously illustrated, yours for only $4.50.

BOVINE TUBERCULOSIS

By John Francis, B.Sc., M.R.C.V.S., here's a priceless hand book for the Veterinary Surgeon, medical worker interested in the study of safe dairy products, for the researcher comparing tuberculosis pathology. These 220 pages of comprehensive data with convenient tables, references and illustrations cover the history and distribution of the disease and various methods of vaccination. Yours for only $4.50.

TUBERCLE

A convenient way to keep abreast of tuberculosis topics, here is the official journal of the British Tuberculosis Association. Published for 80 years, this notable monthly is regarded as one of the leading periodicals devoted exclusively to every aspect of tuberculosis and ancillary diseases. Yearly subscription only $6.00.
Order one or all three NOW! (Money back guarantee)

Staples Press, Inc.
Dept. AR.T. 1
70 East 45 Street, New York 17, N. Y.

Maryknoll
SANATORIUM
(Maryknoll Sisters)

MONROVIA, CALIFORNIA

• A Sanatorium for the treatment of tuberculosis and other diseases of the lungs. Located in the foothills of the Sierra Madre Mountains, Southern exposure. Accommodations are private, modern, and comfortable. Rates are moderate. General care of patient is conducive to physical and mental well being.

SISTER MARY PIETA
Superintendent

E. W. HAYES, M.D.
Medical Director

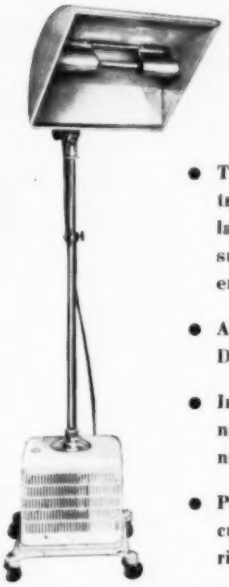
Doctor:

When your patients require ultraviolet irradiation we suggest you prescribe with confidence the

HANOVIA ULTRAVIOLET QUARTZ LAMP

(Prescription Model)

The Most Efficient in Performance and Results



Ideal for post operative recuperation and convalescence.

- **The Hanovia Ultraviolet Quartz lamp outdoes the sun in ultraviolet energy.**
- **Activates Vitamin D—Nature's way.**
- **Invaluable for prenatal care and to nursing mothers.**
- **Prophylactic and curative effect on rickets.**
- **Assists children in the growth of sturdy limbs and sound teeth.**
- **Stimulates the blood-building centers of the body.**
- **Helps keep the hemoglobin and red blood cells at the full heathful level**

Available through your local surgical supply house.

For descriptive folder address Dept. AR-11-49

HANOVIA Chemical & Mfg. Co.

NEWARK 5, N. J.

OAK RIDGE SANATORIUM

GREEN SPRINGS, OHIO

for
TUBERCULOSIS

•

Diagnosis
Treatment

•

SITUATED in the beautiful springs country of Northern Ohio, this modern Sanatorium offers not only up-to-date treatment for all forms of Tuberculosis but a setting of utmost beauty and restfulness for the convalescent. General Hospital Facilities with complete Surgery . . . Modern Steam-heated Rooms . . . Graduate Nurses . . . Personal Care for Every Patient.

Natural Mineral Spring
(8,000,000 gallons per day.)
Artesian Well

Reasonable rates

PAUL M. HOLMES, M.D., Medical Director
JOHN J. GEDERT, M.D., Resident Physician
GEO. S. BOWERS, M.D., Internist
ELEANOR BLIVEN, R.N., Supt. Nurses
ALEX C. JOHNSON, Pres. & Gen. Mgr.
M. M. RIDDLE, M.D., Eye, Ear, Nose and Throat
WM. NEILL, M.D., Thoracic Surgeon
OTTO MUHME, M.D., Thoracic Surgeon

1950 National Tuberculosis Association Annual Meeting
Washington, D. C.

The Annual Meeting of the National Tuberculosis Association will be held in Washington, D. C. April 24–28, 1950. Meeting sessions will be held in the Hotel Statler.

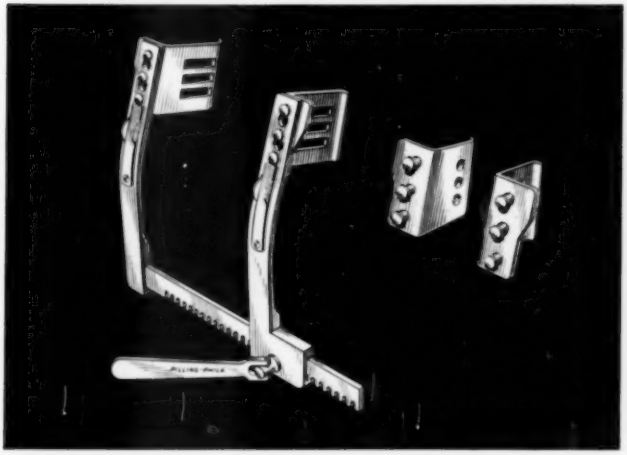
Some 920 rooms have been promised by the hotels listed below for the accommodation of those attending the meeting. Only a limited number of single rooms will be available.

Application for room reservations should be made directly with the hotel of your choice and should be made for double rooms wherever possible.

HOTEL	*ADDRESS*	*SINGLE*	*DOUBLE*
STATLER	16th & K Streets, N.W.	$5.00–$11.50	$8.00–$12.00
AMBASSADOR	14th & K Streets, N.W.	3.50– 6.00	6.00– 8.00
BLACKSTONE	1016 17th Street, N.W.	4.00– 5.00	6.00– 7.00
HAMILTON	14th & K Streets, N.W.	4.00– 5.50	6.00– 7.00
HAY-ADAMS	16th & H Streets, N.W.	4.50– 7.00	6.50– 8.00
LAFAYETTE	16th & Eye Streets, N.W.	5.00– 7.00	7.00– 10.00
MARTINIQUE	16th & M Streets, N.W.	4.00– 6.00	6.00– 8.00
SHERATON	15th & L Streets, N.W.	3.85– 5.85	6.35– 8.85
WASHINGTON	15th & Pa., N.W.	5.00– 9.00	9.00– 12.00
WILLARD	14th & Pa., N.W.	4.50– 8.00	7.00– 11.00

See February issue of N.T.A. Bulletin for preliminary programs

Authentic Instruments
FOR THE THORACIC SURGEON



BURFORD MODIFICATION OF THE
FINOCHIETTO RIB SPREADER

Thoracic surgeons look to Pilling for the new and important instruments in their special field. Since 1814, leaders in this field have consulted Pilling and designed instruments to fit their exacting requirements, confident in their knowledge that Pilling craftsmen would create the instruments they desired.

A fine example of Pilling craftsmanship is the Finochietto Rib Spreader, originally designed by Professors Henrique and Ricardo Finochietto of Buenos Aires. Now, the modification of this popular instrument by Thomas H. Burford, M.D., Barnes Hospital, St. Louis, provides even greater versatility. By properly switching the two pairs of interchangeable blades, the instrument can be used as medium or large size, or combinations of one large and one small blade. The shafts are also curved to conform to body curvature, thus keeping the spreader out of the operator's way.

ORDER instruments direct from

George P. Pilling and Son Company

3451 WALNUT STREET
Philadelphia

A Standing Invitation: When in Philadelphia, visit our modern sales rooms and manufacturing plant. Free parking on our private lot.

INSTRUMENTS BY— Pilling

PILLING FOR PERFECTION in surgical instruments

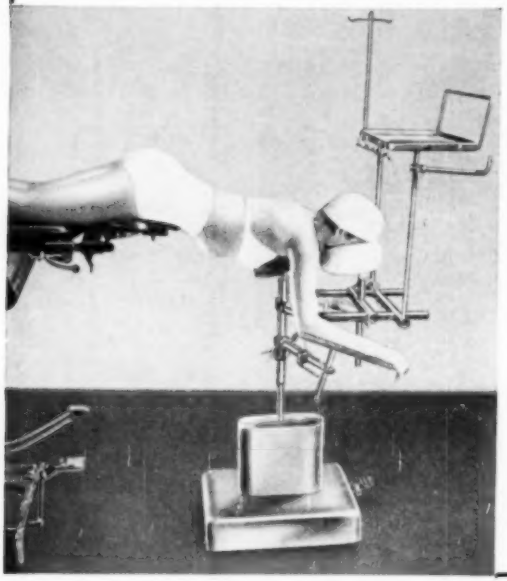
SAROT
Bronchial Clamp
Available in pairs—right and left

SAROT
Intra-Thoracic Artery Clamp

SATINSKY
Scissors

SATINSKY
Vena Cava Clamp

The NACLERIO SUPPORT *for*



Prone-Position Surgery

used in conjunction with any standard operating table, to keep maximum vital capacity, prevent contralateral spillage, and provide ideal access for surgery, with all favorable variations of the patient's position.

SIMPLE—PORTABLE—
INEXPENSIVE—VERSATILE
Write for Circular

J. H. EMERSON CO.
22 COTTAGE PARK AVENUE
CAMBRIDGE 40, MASSACHUSETTS

Makers of EMERSON
LUNG IMMOBILIZERS

EUDOWOOD SANATORIUM
Towson, Maryland

A modern, thoroughly equipped institution for the treatment of tuberculosis. Located on a large 350-acre farm in the beautiful, healthful Maryland countryside. All city conveniences . . . eight miles north of Baltimore . . . one mile east of Towson, Maryland.

Private rooms with adjoining baths . . . $7.00 and $8.00 per day, including general nursing and medical attention. *For further information, address:*

DR. WILLIAM A. BRIDGES, *Superintendent*
Eudowood, Towson 4, Maryland

Which Forms of PARASAL PAS, Para Aminosalicylic Acid Are You Using in Your TB Clinical Trials?

AT THE present writing (Nov. 14, 1949) some 200 sanitaria, hospitals and specialists are clinically testing the therapeutic activity of PARASAL —Panray's brand of PAS. Hundreds of case histories have already been taken, and the reports are continuing to show a definite trend.

IS PARASAL really effective? The evidence now indicates that (1) PARASAL *alone is a valuable therapeutic agent in the treatment of several forms of tuberculosis,* and that (2) *it is especially indicated as a synergist to streptomycin therapy.**

*REF.: 8th Streptomycin Conference, Nov. 13, 1949, Atlanta, Ga.

IN RESPONSE to widespread demand, Panray has developed, and now offers for further investigational use, *eight* forms of PARASAL. One of these, in all probability, will meet *your* particular requirements:

- ☐ PARASAL POWDER (Para Aminosalicylic acid).
- ☐ PARASAL SODIUM POWDER (Sodium para aminosalicylate dihydrate).
- ☐ PARASAL TABLETS (0.5 gm.) Acid or sodium salt.
- ☐ PARASAL TABLETS, ENTERIC COATED (0.5 gm.) Acid or sodium salt.
- ☐ PARASAL GRANULES, ENTERIC COATED (acid only).
- ☐ PARASAL OINTMENT for topical application.
- ☐ PARASAL AMPULES. Sodium salt solution, for intravenous administration.
- ☐ PARASAL BULK SOLUTIONS. Sodium salt in sterile solution for local administration.

Write for bibliography, prices, and descriptive literature

PARASAL is manufactured by Hexagon Laboratories, Inc., distributed exclusively by:

THE PANRAY CORP.

Custom Manufacturers of Fine Organic Chemicals

340 Canal Street New York 13, N. Y.

Every WHITE KNIGHT HOSPITAL GARMENT

is Designed and Tailored to Meet the *Exacting Demands* of Hospital Service

IN designing and tailoring WHITE KNIGHT Hospital Garments, whether they happen to be Patients' Gowns, Operating Gowns, Nurses' Uniforms, or Infants' Gowns...the specific and exacting requirements of each type of service must in all cases be both the starting point and the climax.

Only the most intimate experience and knowledge of hospital service needs can create wholly satisfactory final results. This is a goal that Will Ross, Inc., has not only strived to attain but has translated into accomplished fact.

The White Knight label is a symbol of the best that can be produced — in terms of excellence of materials, craftsmanship and, above all, utility without equivocation.

The Will Ross Unconditional Guarantee applies to White Knight Hospital Garments just as it does to several thousand other hospital necessities that add to the ease, efficiency and economy of broad service to the sick and injured.

A Patient's Gown is a simple thing. But in its very simplicity there is a story — based upon the fundamental purpose of the garment. It must be *comfortable* in use and easy to put on and take off without inconvenience or discomfort to the patient. The patient's body must be quickly and fully accessible to receive the attentions required from nurses and attending physicians. The garment must protect and cover . . . yet provide complete freedom of action. It must be made of materials that will stand a great deal of hard wear and frequent launderings. Both initial and upkeep cost must be low.

The same is true of Operating Gowns, Nurses' Gowns, Children's and Infants' Gowns and other Hospital Garments and Accessories. It is the knowledge of this fact and the continuous application of this knowledge that makes White Knight Hospital Garments good in every sense of the word.

WILL ROSS, INC., Milwaukee 10, Wisconsin

1914 1949

35 YEARS OF SERVICE TO HOSPITALS

Manufacturers and Distributors of Hospital and Sanatorium Supplies and Equipment

THE SURGICAL TREATMENT OF RECURRENT AND CHRONIC SPONTANEOUS PNEUMOTHORAX OF NONTUBERCULOUS ORIGIN[1]

RICHARD H. MEADE, JR., AND BRIAN B. BLADES

(Received for publication July 29, 1949)

INTRODUCTION

Spontaneous pneumothorax is a familiar subject to all who are interested in chest disturbances. The frequency with which it occurs in apparently healthy people, and its usually benign course in such instances, is in striking contrast to its appearance in cases of far advanced tuberculosis. In the latter, spontaneous pneumothorax is of serious import and not infrequently is a landmark on the road to death. In this group the underlying disease is of paramount importance. In the nontuberculous cases there is frequently no serious underlying disease.

Spontaneous pneumothorax of nontuberculous origin may be grouped into three simple classes. In the first are those cases in which there is a single attack from which the patient recovers without incident or sequellae. In the second group are those in which there are recurring attacks. These may be of short duration, interfere little with the patient's activities, and require little treatment, or they may require aspiration of the air. In some cases, however, the pneumothorax persists for weeks or months and makes the patient an invalid. These require some form of treatment that will prevent the recurrence of the pneumothorax after re-expansion has been obtained. In the final group are cases in which a pneumothorax develops and the lung fails to re-expand spontaneously or after repeated aspiration of air. For these, the writers believe open operation should be used although many cases have been reported in which re-expansion has followed the induction of a chemical pleuritis.

Since Spengler (6) in 1906 suggested the use of silver nitrate injections to induce a chemical pleuritis to prevent the recurrence of pneumothorax of nontuberculous origin, this and various other agents have been used with considerable success. The underlying pathology in such cases has usually been a localized area of emphysema or scattered emphysematous blebs on the surface of the lung. In 1939, Hennell and Steinberg (4) reported the successful treatment of 5 cases of recurrent and chronic, tense pneumothorax by means of injections of glucose, iodized oil, or one followed by the other. Brock (3) in 1948 reviewed the subject of the treatment of these forms of pneumothorax and reported the largest series of cases in the literature. Among 71 cases of spontaneous pneumothorax of nontuberculous origin, he presented 46 chronic cases and 25 recurrent ones. In 8 of the chronic cases there were large cysts which required excision, or lobectomy. All of the others were treated by the induction of a pleuritis with silver nitrate. The treatment proved successful in all cases.

[1] From the Chest Surgical Services of Walter Reed General Hospital and of Kennedy General Hospital.

In the present communication, 18 cases of spontaneous pneumothorax are presented. In 8 the pneumothorax was recurrent, in 11 it was chronic. Operation was performed in all. Three of the chronic cases had bronchiogenic cysts which had to be excised, or treated by lobectomy. In 6 of the chronic cases it was necessary to do decortications of the lung in order to bring about its expansion. A brief report of these cases will be given and the management of these forms of pneumothorax will be discussed.

Origin of nontuberculous pneumothorax: The origin of the usual case of spontaneous pneumothorax not due to tuberculosis is the rupture of a peripheral air sac in the presence of a free pleural space. Such dilated alveoli are known to occur frequently in normal lungs. Their rupture as the result of a sudden increase in intra-alveolar pressure is not remarkable. When this event is not associated with the presence of some inflammatory process in the underlying lung or pleura, there is collapse of the lung and the leak becomes sealed. The ruptured area heals and the lung re-expands. When there is underlying emphysema, or some chronic inflammatory process, the decrease in vital capacity may be severe. However, unless the air is leaking from an involved area, it tends to stop quickly and the lung re-expands. Ruptures of areas in parts of the lung affected by active inflammatory processes will usually result in a pyopneumothorax, or hemopneumothorax, which will not be considered in this presentation.

Observations

The management of cases of recurrent pneumothorax of short duration usually does not involve surgical procedures. Conservative measures usually suffice. These include the injection of various irritating substances, such as silver nitrate, glucose, and iodized oil, after it has been demonstrated that the lung can re-expand.

The cases of recurrent pneumothorax of longer duration can be more certainly cured by open operation, as the underlying cause of the leak can be corrected and provisions made for maintaining the expansion of the lung. Eight of our patients had this type of recurring pneumothorax, and all were subjected to operation. They had pleural poudrage with talc and sulfanilamide, had this in combination with resection of the leaking emphysematous blebs, or had simple excision of the blebs.

Chronic pneumothorax means that the lung remains collapsed and shows no tendency to re-expand. There were 11 patients in this group. Although tuberculosis was suspected and searched for in each case, it was not found. In general, the two main causes of the pneumothorax were the persistence of a bronchopleural leak, and/or the encasement of the collapsed lung in adhesions, or an inelastic membrane which prevented its re-expansion. These factors will be considered in the presentation of the individual cases.

In presenting our cases we shall group them according to the type of pneumothorax and according to the underlying etiological factors. Only the essential features will be given and the illustrations will be limited to examples of the different types of cases. With one exception, all of the cases being reported were seen in army hospitals during the last war. Long follow-up studies have not been

possible in every case, but they are considered to have been of sufficient length to allow for a reasonably satisfactory evaluation of the results. In no instance have we been aware of the recurrence of the pneumothorax after our surgical treatment. There were no deaths and no serious complications.

RECURRENT SPONTANEOUS PNEUMOTHORAX

Eight patients who had recurrent, spontaneous pneumothorax were treated by open thoracotomy. In none of them was there evidence of any underlying chronic disease. In 3 instances no cause for the pneumothorax could be found. In the other 5 cases emphysematous blebs were thought to be the source of the pneumothorax.

Etiology Unknown

Of the patients in whom no etiological factor could be found, the first was 21 years old and had had five recurrences of his pneumothorax within three years. The second also was 21 years old and had had two attacks in one year. The third was 23 years old and had had three attacks in two years. They were operated upon and, after it was determined that the lung could fully re-expand, the entire pleural surface was dusted with talc mixed with 0.3 Gm. to 10 Gm. of sulfanilamide crystals. The chest wall was then closed without drainage. The lungs remained expanded and there was no need for thoracentesis. They were followed for periods of ten, twelve, and seventeen months without signs of recurrence.

Emphysematous Bleb

In the next group of patients a single emphysematous bleb was considered to be the etiological agent in one, and in the other there were four blebs (figures 1 and 2). The first patient was 26 years old and had had three attacks of pneumothorax between November 1942 and May 1943. The second was 29 years old and had had four attacks between January 1943 and December 1944. In both cases the blebs were excised and the defects sutured. After complete re-expansion of the lung, the chest wall was closed in layers without drainage. In neither case was aspiration of the chest necessary after the operation. No long time follow-up was possible in either case, but it was extremely unlikely that there was a recurrence as the men were still in the army and would have been referred back to one of us if there had been any further trouble.

In the final group of cases of recurrent pneumothorax, the lungs were found to have so many blebs on their surfaces that removal of them was not attempted. Instead, the pleural surfaces were dusted with talc and sulfanilamide after it had been demonstrated that the lungs could be fully expanded, and the chest wall closed without drainage. The first patient in this group was a 51-year-old woman who had had three recurrences in fourteen months. Her left upper lobe was found to be covered with small blister-like blebs. She needed no thoracentesis after operation and was followed for eight months without evidence of recurrence. The second patient was a 27-year-old man who had had four attacks

of pneumothorax in eight months. His left upper lobe was found to be partly covered with small blebs. Following his operation, his pleural cavity had to be aspirated once. He returned to military duty and had no recurrence during the twenty months he was followed. The third patient was a 31-year-old physician who had had two attacks in two years. He was operated upon a month after the onset of his second attack and while a small pocket of pneumothorax persisted. His right upper lobe was found to be partly covered with small blister-like blebs and a fistula was seen which was thought to be the site of leakage of the air and to have been due to a rupture of one of the emphysematous blebs. The fistula was closed by suture and the lung found to be completely expandable

FIG. 1. (Left) Roentgenogram of chest of patient with recurrent pneumothorax showing marked collapse of the right middle and lower lobes.

FIG. 2. (Right) Photographs of blebs excised from the surfaces of the right middle and lower lobes of the patient whose roentgenogram is shown in figure 1.

The upper lobe was then "iced" with talc and sulfanilamide and the chest wall closed without drainage. No postoperative thoracentesis was necessary. Although no follow-up was obtained in his case, he was a physician and had been instructed to contact one of us should he have further trouble.

These cases were all recurrent in type, and before operation it was known that the lung could fully re-expand or had fully done so. The problem was to ensure the maintenance of this fully expanded position. By applying irritants to the surface of the lung, an inflammatory reaction was started that resulted in thickening of the visceral pleura to such an extent that further rupture of peripheral blebs could not take place. The possibility that the recurrence of the pneumothorax was prevented by the production of a pleural symphysis must also be considered. Certainly the pleural reaction must produce a temporary symphysis, but that this may not be permanent is seen in many cases of empyema in which,

even after surgical drainage, full restoration to normal seems to occur. Also cases of pneumothorax have developed after apparent recovery from an empyema. Hennell and Steinberg (4) report a case in which, following the disappearance of fluid from the chest of a patient with a drained, postpneumonic pyopneumothorax, the pneumothorax persisted until a chemical pleuritis was created by the injection of iodized oil. This case would seem to indicate that the closure of the bronchopleural fistula by the chemically induced pleuritis was more important than the normal tendency to pleural symphysis as the result of the preexisting empyema.

CHRONIC SPONTANEOUS PNEUMOTHORAX

The cases of true, chronic spontaneous pneumothorax, in which it was impossible to bring about re-expansion of the lung before operation, numbered eleven and can be conveniently divided into two main groups. In the one were those in which a definite source for the pneumothorax could be found and, in the other, those in which it was impossible to determine its origin.

Source of Pneumothorax Known

The cases for which a definite source of the pneumothorax could be found included 3 in which there was a leaking bronchogenic cyst, one with a leaking emphysematous cyst, one in which a band adhesion apparently maintained the patency of a bronchopleural fistula, and 4 in which small leaks in the surface of the lung could be detected.

Rupture of pulmonary cyst: The cases in which the cause of the pneumothorax was most obvious were those in which there had been a rupture of a pulmonary cyst. In 3 the cysts were bronchiogenic, and in one they were emphysematous. In the bronchiogenic ones the problem was merely that of removing the cyst. In 2 it was possible to do so without sacrifice of lung tissue, but in one it was necessary to do a lobectomy. In none of these were there any adhesions which interfered with the re-expansion of the lung. In the case of the emphysematous cysts the chief obstacle to re-expansion of the lung was its encasement by binding adhesions.

The first of the group, chronologically, was a 31-year-old man who had had a pneumothorax for six months before operation. In addition to dyspnea, he had had hemoptysis, cough productive of pus, fever, and chills for the first six weeks. At operation the left upper lobe was found to be largely replaced by a cyst which had ruptured and from which air had escaped. The upper part of the lower lobe was studded with small cysts. The upper lobe was resected and closed drainage of the chest established. His lung promptly expanded to fill his chest but roentgenograms showed evidence of a cyst in his opposite lung, which had not been apparent before operation. Pyelographic studies revealed apparently incomplete rotation of his kidneys and bizarre deformities of the pelves and calyces. The study of the resected lobe and these other findings would place this case in the group of true congenital cystic disease of the lungs. He was examined nineteen months after the operation and found to have no evidence of further

chest disease. A year later he still had no evidence of recurrence of his pneumothorax.

The next 2 patients with bronchiogenic cysts were diagnostic problems, but their management was simple. The first was 46 years old and his symptoms were all gastrointestinal; the pneumothorax had persisted for four months before his operation. Closed thoracoscopy showed a large cyst collapsed against the surface of the deflated right lung. At operation one month later, the cyst was found to be intact and occupying the entire pleural cavity. It arose from the upper lobe near the origin of the bronchus to this lobe. Its walls contained islands of cartilage and the lung around the base of the cyst felt as if it contained an abnormal amount of cartilage. The cyst was excised with a minute amount of lung tissue and the chest wall was closed without drainage after the lung had been fully expanded. No postoperative aspiration of the chest was necessary, and the lung remained expanded up to the time he was last seen, two months after the operation.

The third of the patients with bronchiogenic cysts had symptoms suggesting coronary arterial disease. He was 40 years old and his first attack of severe substernal pain, with radiation to the left arm, was relieved by nitroglycerine. No roentgenogram of the chest was taken at the time, but an electrocardiogram was made which showed no abnormality and he was returned to duty. This was in March 1944. Another attack occurred in seven months and again the electrocardiogram was normal, but this time a roentgenogram of the chest was made which showed evidence of a cyst, or a localized pneumothorax. Two months later at Kennedy General Hospital, studies showed no evidence of heart disease but the roentgenogram showed a pneumothorax in the right upper chest. Closed thoracoscopy revealed a pneumothorax and a partly collapsed cyst arising from the right upper lobe. Four days later the cyst was resected by cutting across a base of normal-looking lung tissue. The middle lobe was seen to have a smaller lobe projecting from its lower anterior surface, and the lower lobe was almost completely divided into two. One of the lower lobes was retrocardiac in position. There was no evidence of anthracosis in this lung in spite of the fact that the patient had lived in cities most of his life. His convalescence was uneventful, and three months later his lung was still fully expanded and he had had no more symptoms of any kind.

The final patient in this series was a 55-year-old Russian plumber. In the evening, following a strenuous afternoon in which he had lifted a heavy boiler, he suddenly became short of breath. Not until ten days later was the cause for his dyspnea found when a roentgenogram of his chest showed an extensive pneumothorax. Repeated aspiration of the air only gave temporary relief and he had continued as a chronic invalid. He was first seen by one of us five months later. He was found to have an extensive pneumothorax (figure 3). Before operating on him it was decided to try the effect of continuous decompression. This only resulted in his developing an extensive interstitial emphysema as the air under pressure escaped along the tract of the needle. Apparently, the fixation of his mediastinum and the presence of adhesions binding his lung to a part of the chest wall saved him from the usual effects of a tension pneumothorax.

When he was operated on six days later the lung was collapsed except for extensive attachments of the upper lobe to the lateral chest wall. There were a

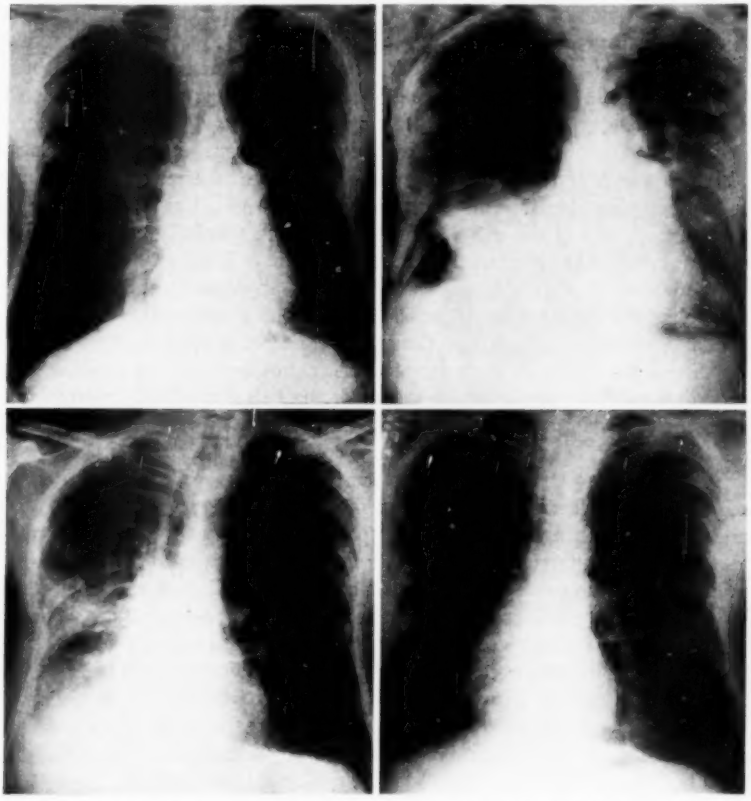


FIG. 3. (Upper left) Roentgenogram of chest of patient with chronic pneumothorax due to rupture of a large emphysematous cyst. Adhesions prevent the complete collapse of the upper lobe.

FIG. 4. (Upper right) Roentgenogram of the chest of the same patient the first morning after the operation showing the lung symmetrically collapsed and marked interstitial emphysema.

FIG. 5. (Lower left) Roentgenogram of the same chest five days after operation, showing complete re-expansion of the right lung and a small amount of interstitial emphysema.

FIG. 6. (Lower right) Roentgenogram of the chest of the same patient eighteen months after his operation. No abnormalities are noted except for the rib defect produced by the operation.

number of large cysts buried in the lung and air was found to be escaping from the largest one. The opening was not obvious. Although the only way in which the cysts could be eradicated was by total pneumonectomy, this was not possible

as there were thought to be large cysts in the opposite lung. Accordingly, the lung was decorticated and the cystic areas infolded into the normal appearing lung surrounding them. Attempts to suture the area from which the air was thought to be escaping were futile but the area was infolded as were the cysts. Following these procedures the lung could be expanded without interference, but full expansion was not attempted because of the danger of tearing the sutured areas. Closed drainage was established with a single tube which was connected with a water trap.

Four hours after the operation he had developed extensive interstitial emphysema which was progressive and only came under control after another drainage tube had been inserted into his pleural cavity (figure 4). From then on he rapidly recovered, and at the end of five days the lung was fully expanded (figure 5) and has remained so ever since. A roentgenogram of his chest eighteen months after the operation (figure 6) shows the present appearance of his chest. This case emphasized the need for decortication in such cases of chronic pneumothorax, and more especially showed the need for really adequate closed drainage when the source of a tension pneumothorax cannot be definitely eradicated.

Among the other cases in which it was thought that a definite source for the pneumothorax could be demonstrated, the first was a 37-year-old man who had had three attacks of pneumothorax during a period of six months and whose lung had shown no tendency to re-expand following the last episode. Roentgenograms of his chest showed an extensive pneumothorax on the right with a band adhesion running from the upper part of this lung to the chest wall. On thoracoscopy the adhesion was seen to be arising from a rather normal-looking area of lung and no evidence of a fistula could be found. The adhesion was divided and the lung collapsed symmetrically. Gradual re-expansion of the lung occurred and the patient was discharged with a normal-appearing chest roentgenogram. No follow-up observations have been obtained in this case although he was operated upon in November 1943. The persistence of the pneumothorax in this patient was thought to be due to the rupture of a peripheral bleb and the maintenance of the patency of the opening by the attachment of the adhesion to the edge of the defect. Although no fistula could actually be seen, the sequence of events would tend to support the hypothesis advanced. In cases of tuberculosis, tension pneumothorax has been successfully treated in this manner in a number of cases.

Peripheral fistula or bleb: There were 4 cases in which the persistent pneumothorax was found to be due to definite leak of air from a peripheral fistula or from a peripheral bleb. In each it was possible to close the defect by suture and to bring about re-expansion of the lung. The first of these was a 25-year-old man who was discovered to have a pneumothorax in June 1942. He was carefully studied in two hospitals and efforts were made without success to cause re-expansion of his lung. He was finally operated upon in December 1943. A small bleb was found on the extreme apex of the right upper lobe from which air could be seen to escape when this area was covered with normal salt solution. The area was inverted with catgut sutures and further covered with a piece of

muscle which was held in place by "tissue glue" (Sano (5)) made from a suspension of the patient's red blood cells and plasma. This "tissue glue" was also applied to the entire surface of the upper lobe and the adjacent parietal pleura. The pleura elsewhere was vigorously rubbed with dry gauze to produce a pleuritis. The lung was inflated and the chest wall closed without drainage. Small amounts of fluid had to be aspirated from the pleural cavity on two occasions, and the lung gradually completely re-expanded. He was returned to active duty in the army and fourteen months later reported that he was in excellent health and had had no further attack of pneumothorax.

The next patient in this group was 34 years old. He had had his pneumothorax for five months and, after all attempts to bring about re-expansion had failed, he was operated upon. His lung was found to be completely collapsed and the air under positive pressure. A bleb was found in the depth of an incomplete fissure between the left upper and lower lobes and air was seen to be escaping from it. This area was buried by means of catgut sutures and further covered with muscle and pleural grafts. Other blebs were seen on the surface of the lung but none allowed the escape of air. The lung could not be inflated because of the presence of an inelastic membrane which covered the posterior and medial aspects of the lung. This was incised and peeled off the lung, allowing it to re-expand. Closed drainage of the pleural cavity was established and the chest wall closed. Re-expansion of the lung promptly occurred, and he was returned to duty. He was followed for six months without evidence of recurrence.

The third member of this group was a young man who had had a pneumothorax of varying extent for more than a year before being admitted to Kennedy General Hospital in June 1944. All attempts to re-expand the lung having failed, he was operated upon and the lung found to be adherent posteriorly. A definite, small opening was found in the midst of a roughened area on the anterolateral aspect of the left lower lobe from which air was escaping. This area was closed with interrupted sutures of fine silk and re-enforced with two muscle grafts. The lower lobe was prevented from re-expansion by the thick membrane which covered its lower part. This was removed without difficulty allowing the lobe to be fully inflated. Some oozing had persisted from the area in which the fistula had been sutured in spite of the sutures and muscle grafts. Accordingly, a single piece of oxidized gauze (Oxycel) was placed over this area and the oozing promptly stopped. After establishing closed drainage, the chest wall was closed in layers. The lung was slow in re-expanding and required active suction drainage and aspiration of air from the upper part of the pleural cavity before complete re-expansion was established after two months. He was discharged from the hospital in November 1944. A roentgenogram of the chest in September 1946 showed no abnormalities and he was seen in March 1947 after having had no further recurrence of his pneumothorax.

The last in this particular group was a 35-year-old man admitted to Kennedy General Hospital with a spontaneous pneumothorax of four months' duration (figure 7). Repeated aspiration had failed to have any effect on the pneumothorax. An exploratory thoracoscopy showed the lung to be nonexpansile

but no fistula could be seen. Three weeks later he was operated upon and the lung was found to be encased in an inelastic membrane (figure 8) and near the

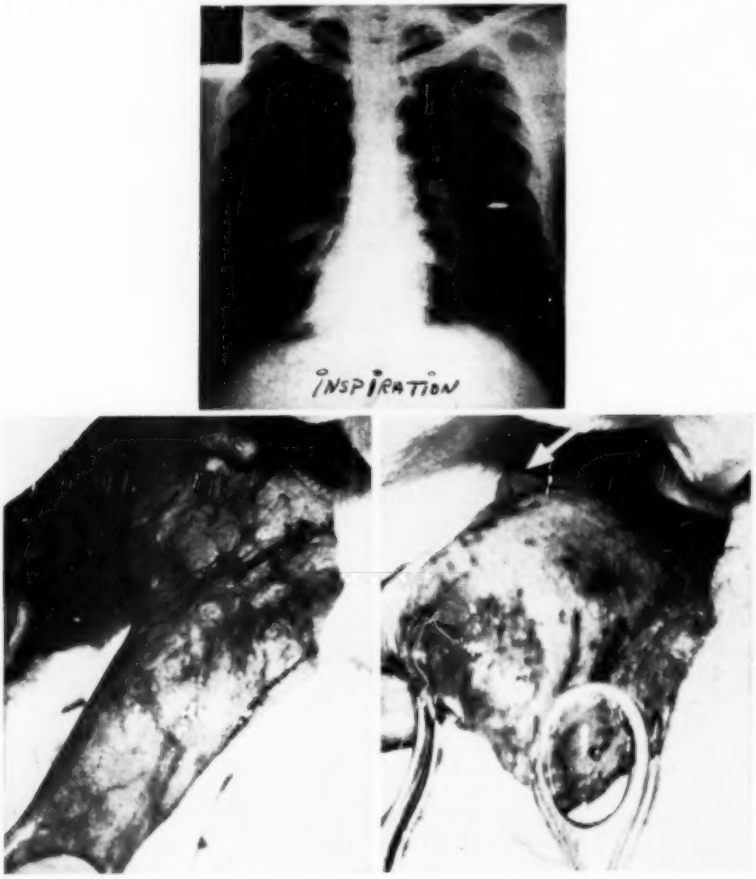


FIG. 7. (Top) Roentgenogram of the chest of a patient with chronic pneumothorax due to a ruptured emphysematous bleb.

FIG. 8. (Lower left) Photograph of the lung at operation showing the lower part of the lung encased in an inelastic membrane which prevented its expansion.

FIG. 9. (Lower right) Photograph of the lung at operation showing the bleb from which air was escaping.

apex of the upper lobe was an emphysematous bleb that ballooned out when the intrabronchial pressure was raised (figure 9). Although no air was seen to escape from this bleb, it was thought that it probably was the source of the pneumothorax and this area was buried in the lung parenchyma by means of

interrupted sutures of fine silk. Because of its encasing membrane the lung could not be expanded until a decortication had been done. This was accomplished by actual removal of the membrane in large pieces and by incising the membrane in other areas and causing it to split further by active expansion of the underlying lung. Complete re-expansion was obtained. Closed drainage was used and the lung rapidly filled the pleural space and remained expanded. Two years later he had a spontaneous pneumothorax in the opposite chest from which he promptly recovered.

These 4 cases all showed evidence of the source of their pneumothorax, and in 3 the lung could not be expanded until after a decortication had been done. In each of these cases the chief barrier to spontaneous re-expansion was the presence of the inflammatory capsule, or of an adhesion.

Source of Pneumothorax Unknown

The other main division of our cases of chronic pneumothorax was made up of 2 in which no source for the pneumothorax could be found, but in each of which the lung was prevented from re-expanding by binding adhesions or a covering membrane. The first was a 23-year-old man who had had an acute upper respiratory infection followed by pleurisy with effusion. The effusion cleared but he was left with a chronic pneumothorax. Seven months later he was admitted to Kennedy General Hospital. After exhaustive studies to determine the etiological factor had proved fruitless and repeated aspiration of air had had no effect on the pneumothorax, he was operated upon, thirteen months after the onset of his illness. At operation no source for the pneumothorax could be found, but there were dense adhesions binding the lower lobe to the diaphragm and paravertebral region. After dividing these adhesions, the lung could be fully expanded. Closed drainage was established and the chest wall closed in layers. Drainage had to be maintained for two weeks before the lung fully expanded. Because of the symptoms of a psychoneurosis, he was kept under observation for four months before discharge and there was no recurrence of the pneumothorax during this time. Attempts to follow him have been unsuccessful. It is believed that the pneumothorax developed during the period of the acute pneumonitis, that the effusion added to the collapse of the lung, and that the associated pleuritis fixed the lung and prevented its re-expansion after the active infection had subsided. The fluid was absorbed but the air remained.

The other patient in this small group also was 23 years old but he had never had any illness prior to the discovery of his pneumothorax. This discovery took place overseas and he was returned to this country when the lung failed to re-expand. Attempts to bring about re-expansion by repeated aspiration of the air proved ineffectual and he was operated upon five months after the onset of the pneumothorax. At the operation no evidence of a fistula could be found or of any area from which it seemed air might have escaped. The lung was encased in an inelastic membrane (figure 10). Decortication was easily done and the lung completely reinflated (figures 11 and 12). Closed drainage was used for a short time and the lung promptly re-expanded and remained so. One year later

he wrote that he had been working for some months and had had no further trouble.

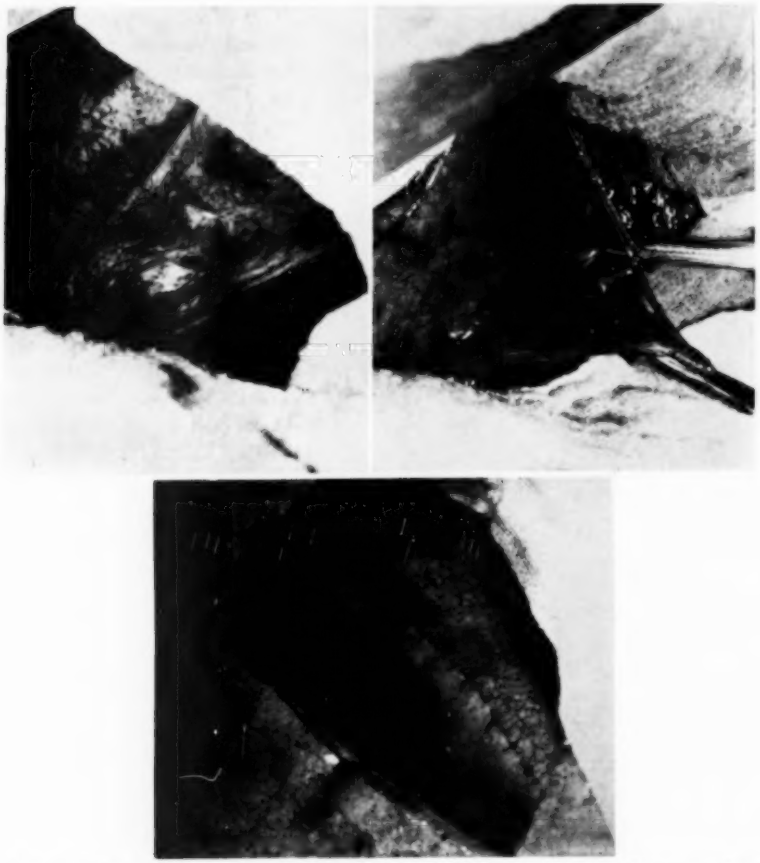


FIG. 10. (Upper left) Photograph of the lung at operation of patient with pneumothorax showing the collapsed lung encased in a membrane.

FIG. 11. (Upper right) Photograph at operation showing the membrane being stripped from the surface of the lung.

FIG. 12. (Bottom) Appearance of the lung after the decortication showing its normal markings.

DISCUSSION

In the cases of recurrent pneumothorax in the present report, it seems apparent that the etiological factor was the rupture of a peripheral bleb. Following this rupture and the establishment of a pneumothorax, the lung collapsed and

the site of air leakage became sealed. Re-expansion then occurred. The ensuing pleural reaction was not sufficiently great to prevent rupture of other blebs, however, or to produce symphysis of the pleural leaves and, when the intra-alveolar pressure again became suddenly increased, the same bleb or another ruptured and pneumothorax again appeared. The problem of the management of these cases was that of preventing further leaks from the lung and maintenance of the lung in its fully expanded state. It cannot be denied that good results in certain cases have been achieved by the induction of a chemical pleuritis with silver nitrate, iodized oil, concentrated glucose solution, and by closed pleural poudrage with talc. Nevertheless, it has been our belief that in cases of recurring pneumothorax of long standing, the open operative approach offers more certain success. Such an approach allows for the direct study of the involved lung and definitive management of the presenting lesion. Although a wide range of vision may be afforded through the use of the thoracoscope, the exploration can never be as complete as when the chest is widely opened.

Among the 11 cases of chronic pneumothorax, the site of leakage of air was apparent in 9 of them. The rupture of large bronchiogenic or emphysematous cysts occurring in 4 of the 9 cases was an obvious cause for the pneumothorax, and the size of the bronchial communication easily accounted for the chronicity. At the same time, however, the size of the fistula should have allowed for infection of the pleural space of sufficient degree to produce an effusion. In none of the 3 cases with bronchiogenic cysts was this true. In the case with emphysematous cysts there had been a pleural reaction of sufficient degree to produce binding adhesions, although at no time was there evidence of an effusion. These adhesions would have been sufficient in themselves to prevent the lung from re-expanding even had the leakage of air stopped. In 4 other patients air could be seen to escape from the lung surface, either from an emphysematous bleb or from an area of localized induration in the lung. In the patient who had had a band adhesion divided by the closed method, no definite fistula was demonstrated, but the progress of the case and its similarity to certain cases of tension pneumothorax occurring in patients with tuberculosis make it seem most likely that a fistula had been held open by the adhesion. Healing of the fistula occurred after the lung had been allowed to completely relax, and the pleural reaction produced by the operative procedure caused the lung to adhere to the parietal pleura and should ensure against a recurrence of the pneumothorax.

In the cases of chronic pneumothorax in which no definite site of leakage could be found, it must be assumed that during the time when the air was leaking from the lung an inflammatory process was in progress which caused the formation of adhesions which later prevented the lung from re-expanding. The first of these patients had a definite pleural effusion before there was evidence of his pneumothorax. He was treated with sulfonamides during this time and they undoubtedly played an important role in sterilizing the pleural cavity. The other patient had had no evidence of pleural infection at any time and had received no sulfonamides or penicillin.

Aside from the persistence of a bronchopleural fistula, the other important

factor in the pathogenesis of these cases of chronic pneumothorax was the trapping of the collapsed lung by adhesions or its encasement in an inelastic membrane. In 6 of the 11 cases it was necessary to do a decortication before the lung could be made to expand, even when the intrabronchial pressure was raised to a high level. This experience is apparently unique if one is to judge from the literature. Except for Brewer, Dolley, and Evans (2), who reported their experience with 15 cases of chronic, spontaneous pneumothorax at the meeting of the American Association for Thoracic Surgery on March 30, 1949, no other authors have noted the importance of decortication in the treatment of chronic pneumothorax. Brock (3), in his recent excellent article, was able to obtain re-expansion of the lung in each of his 46 cases without the use of decortication. Furthermore, except in 8 cases associated with pulmonary cysts which required excision of the cyst or lobectomy, he simply induced a pleuritis by means of the injection of silver nitrate. Also, Alexander and Haight (1), in the paper they presented before the American Trudeau Society in 1947, cited no case in which it was necessary to do a decortication, although open thoracotomy was done in all of their cases. Why the present writers found 6 cases in 11 who needed decortication to allow for re-expansion of the lungs and Brock (3) found none in a much larger series is hard to understand. Perhaps as our series grows in size, the incidence of incapacitating adhesions will decrease. Certainly the recognition of this condition cannot be certain without open thoracotomy and hence this approach is regarded as preferable.

The object of all therapy is to return the patient to a state of health as safely and as quickly as possible. Conditions in individual cases must always determine the line of treatment. It is also important to realize that radical surgery may at times be more conservative treatment than nonoperative management. In the series of cases of chronic pneumothorax reported by Hennell and Steinberg (4), in which intrapleural injections of glucose or of iodized oil, or of one followed by the other, were employed, the convalescence required from one to six months. In the larger series reported by Brock (3) the duration of convalescence was shorter but the patients had to have repeated chest aspirations, and at times the chemical pleuritis had to be reinduced by further injection of silver nitrate. The longest period of convalescence in any of our cases was two months and most of them were well within two weeks. There has been no recurrence in any of the reported cases, or in our series, and no serious complications.

Summary

1. Eight cases of recurrent spontaneous pneumothorax, and 11 cases of chronic spontaneous pneumothorax of nontuberculous origin, are reported. All were cured by operative intervention.

2. The recurrent pneumothoraces were found to be due to the rupture of peripheral, emphysematous blebs in 5 instances. No cause for the pneumothorax was found in 3 patients.

3. In 2 recurrent cases the blebs were excised. In one, with multiple blebs, a fistula was closed and the pleural surfaces covered with talc and sulfanilamide.

In the remaining 5, 2 had multiple blebs and 3 had none; the pleural surfaces were coated with talc and sulfanilamide.

4. The etiological factors in the cases of chronic pneumothorax were: ruptured bronchiogenic cysts in 3; ruptured emphysematous cysts in one; maintenance of a bronchopleural fistula by the attachment of an adhesion to its edge in one; leakage from emphysematous blebs in 4; and no cause for the pneumothorax could be found in 2 instances.

5. The bronchiogenic cysts were treated by excision of the cysts in 2 cases and by lobectomy in one.

6. The emphysematous cysts were invaginated and the lung decorticated.

7. The adhesion holding open the fistula was divided by the closed method.

8. The cases in which a definite leak could be found were treated by suture of the involved area, and in 3 a decortication of the lung was also done in order that the lung might re-expand.

9. The 2 cases in which no cause for the pneumothorax could be found required decortication before the lung could be re-expanded.

Conclusions

The writers believe that open thoracotomy should be done on all patients with recurrent spontaneous pneumothorax of nontuberculous origin if there is not prompt response to simple aspiration of the air or to the induction of a chemical pleuritis. In all cases of chronic spontaneous pneumothorax of nontuberculous origin, it is believed that operation should be done by the closed method only for the division of isolated adhesions and by open thoracotomy. The open operation makes it possible to deal with the etiological factor and to perform a decortication in those cases in which it is needed. It is believed that binding adhesions play an important role in the chronicity of some cases.

SUMARIO

La Asistencia Quirúrgica del Neumotórax Espontáneo Recurrente y Crónico de Origen no Tuberculosos

1. Los casos comunicados de neumotórax espontáneo de origen no tuberculoso comprenden 8 de la forma recurrente y 11 de la crónica. Todos curaron con la intervención cruenta.

2. Los casos recurrentes resultaron ser debidos a la rotura de flictenas enfisematosas, periféricas, 5 veces, sin que se descubriera la causa en el resto.

3. En 2 casos recurrentes se excindieron las flictenas. En uno, con flictenas múltiples, se cerró una fístula y se recubrieron las superficies pleurales con talco y sulfanilamida. De los otros 5, 2 tenían flictenas múltiples y 3 no tenían flictenas, recubriéndose también las superficies pleurales con talco y sulfanilamida.

4. En los casos de neumotórax crónico, los factores etiológicos fueron: quistes bronquiógenos roturados en 3, quistes enfisematosos roturados en uno, mantenimiento de una fístula broncopleural por la unión de una adherencia a su borde en uno, escurrimiento de flictenas enfisematosas en 4, sin que pudiera descubrirse la causa en 2.

5. Los quistes bronquiógenos fueron tratados por excisión del quiste en 2 y por la lobectomía en uno.

6. Los quistes enfisematosos fueron invaginados, decorticándose el púlmón.

7. La adherencia que mantenía la fístula abierta fué despegada por el método cerrado.

8. Los casos en que pudo localizarse un escurrimiento bien definido fueron tratados por sutura de la zona afectada, y en 3 se practicó ademas una decorticación del pulmón, a fin de que éste pudiera reexpandirse.

9. Los 2 casos en que no pudo descubrirse la causa del neumotórax exigieron la decorticación para que el pulmón pudiera reexpandirse.

REFERENCES

(1) Alexander, J., and Haight, C.: The surgical management of chronic spontaneous pneumothorax, read before the meeting of the American Trudeau Society, San Francisco, June 1947.

(2) Brewer, L. A. III, Dolley, F. S., and Evans, B. H.: The surgical management of chronic spontaneous pneumothorax, read before the meeting of the American Association for Thoracic Surgery, New Orleans, La., March 30, 1949.

(3) Brock, R. C.: Recurrent and chronic spontaneous pneumothorax, Thorax, 1948, *3*, 88.

(4) Hennell, H., and Steinberg, M. F.: Tense pneumothorax: Treatment of chronic and recurring forms by induction of chemical pleuritis, Arch. Int. Med., 1939, *63*, 648.

(5) Sano, M. E.: Skin grafting: New method based on principles of tissue culture, Am. J. Surg., July 1943, *61*, 105.

(6) Spengler, L.: Zur Chirurgie des Pneumothorax, Mitteilung uber 10 eigene Fälle von geheiltem tuberculosem Pneumothorax: verbunden in 6 Fällen mit gleichzeitiger Heilung der Lungen tuberculose, Beitr. z. Klin. Chir., 1906, *49*, 80. (quoted by Hennel and Steinberg)

THE SURGICAL IMPORTANCE OF THE ANATOMICAL DISTRIBUTION OF THE PULMONARY SEGMENTS[1,2]

EDWARD M. KENT

(Received for publication May 5, 1949)

An anatomical understanding of, and a universally accepted nomenclature for, the segments of the lungs are undoubtedly of little interest and importance to the members of the medical profession as a whole. Certainly these subjects have no interest to the lay public whatsoever; nevertheless, those of us present today have a vital interest in both. With the rapid advances which have occurred in the medical and surgical treatment of diseases of the lungs, there has been a correspondingly keen curiosity concerning the detailed anatomy of these structures. For the most part, those who have been bitten by this bug of curiosity, this desire to understand more fully the anatomy of the lungs, have come from the fields of anatomy, broncho-esophagology, phthisiology, radiology, thoracic surgery, and from those interested in any type of disease of the lungs. All have contributed in full measure to the advancement of our knowledge in this sphere.

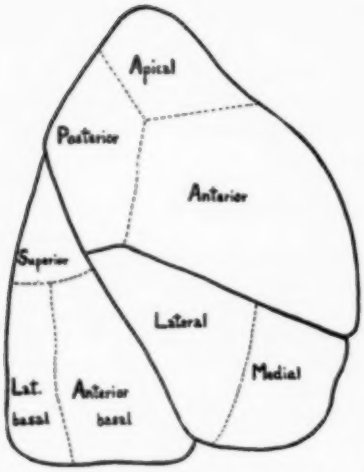
The actual anatomical factors have proved to be universally consistent by the very nature of things, and accordingly, all investigators have agreed rather completely on the distribution of the segments of the lungs. Naturally, as anatomical research continues, we are confronted with an increasing number of anomalies or diversions from the pattern which we have come to accept as normal. Tremenduous contributions have been made in our knowledge of the normal and atypical anatomy of the bronchopulmonary segments by Boyden and his coworkers (1, 2), Brock (3), Churchill and Belsey (4), Foster-Carter (5), Jackson and Huber (6), Scannell (7, 8, 9) and many others.

The matter of arriving at a universally accepted nomenclature for the bronchopulmonary segments has met with many obstacles. There have been numerous classifications offered, some overlapping the others in part, but a few have been quite different and distinctive in terminology. Of course, all have represented the best thoughts on the subject by their various originators. Time simply does not permit a review of the many differing systems of nomenclature in this communication.

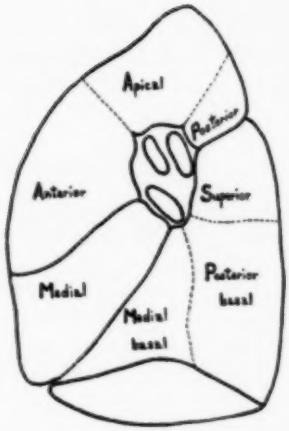
A revised edition of the Diagnostic Standards is in press at this time. When this revision was undertaken, the editors placed the responsibility for the selection of one of the many classifications of the bronchopulmonary segments upon the membership of the American Association for Thoracic Surgery. The choice of this Association has been adopted for inclusion in the revised edition of

[1] From the Department of Surgery, Section of Thoracic Surgery, The University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania.

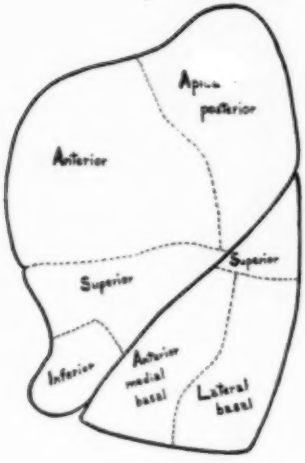
[2] Presented before the Medical Section, as part of the symposium on *Segmental Bronchopulmonary Anatomy*, at the 45th annual meeting of the National Tuberculous Association, Detroit, Michigan, May 5, 1949.



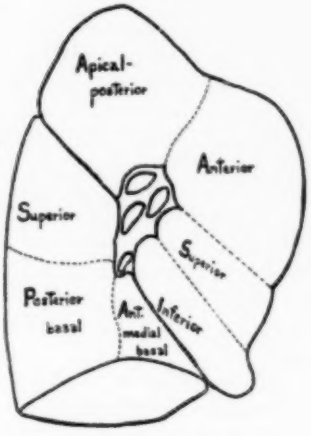
RIGHT LUNG



RIGHT LUNG



LEFT LUNG



LEFT LUNG

FIG. 1. (Upper left) Jackson-Huber classification. Lateral view of diagram of bronchopulmonary segments of the right lung.

FIG. 2. (Upper right) Jackson-Huber classification. Medial view of diagram of bronchopulmonary segments of the right lung.

FIG. 3. (Lower right) Jackson-Huber classification. Lateral view of diagram of bronchopulmonary segments of the left lung.

FIG. 4. (Lower left) Jackson-Huber classification. Medial view of diagram of bronchopulmonary segments of the left lung.

Diagnostic Standards. This considered action of the editors has been sincerely appreciated by the members of the Association for Thoracic Surgery. As a result, careful consideration of the entire matter has been undertaken, first by a specially

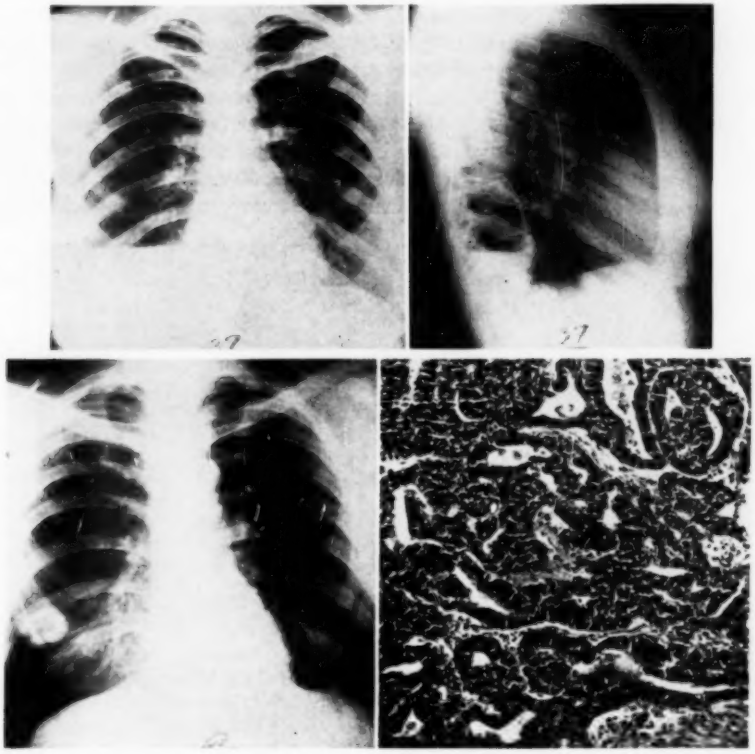


FIG. 5. Solitary pulmonary cyst of right lung: (A) (Upper left) PA view. (B) (Upper right) Lateral view showing position in superior segment of right lower lobe. A segmental resection of this unit was employed to remove the cyst.

FIG. 6. (A) (Lower left) Solitary round lesion in apical segment of right lower lobe. Patient is a 27-year-old male. (B) (Lower right) Segmental resection of superior segment of right lower lobe removed lesion in toto. Frozen section revealed lesion to be papillary adenocarcinoma of metastatic origin. Accordingly, no further resection was performed. Had the lesion proved to be primary pulmonary malignancy, total pneumonectomy would have been performed at this operation. (Note: A primary site has not yet been found.)

appointed committee, and finally by the membership of the Association at the annual meeting in New Orleans in March of this year. The unanimous vote of the Association approved and adopted the Jackson-Huber (6) system of terminology.

In figures 1, 2, 3, and 4 may be seen illustrations of the Jackson-Huber classification. The merits of this nomenclature include consistency, brevity, clarity,

and wide acceptance in this country. Since the necessity of a universally accepted and understood single classification of the bronchopulmonary segments is conceded on all sides, it is fervently to be hoped that universal approval and adoption of the Jackson-Huber nomenclature will follow on this continent, and preferably, in the entire world. We must talk the same language in order that we may understand each other immediately and without the necessity of maintaining in our minds the terminology of numerous, differing classifications.

The surgical application of this knowledge has progressed apace. This has been elaborated upon by Blades (10), Overholt and Langer (11), and by many other contributors. At the present time, the limitations and the over-all scope of this surgical technique have not been explored with finality. All admit that it is of great importance in the surgical treatment of extensive, bilateral bronchiectasis.

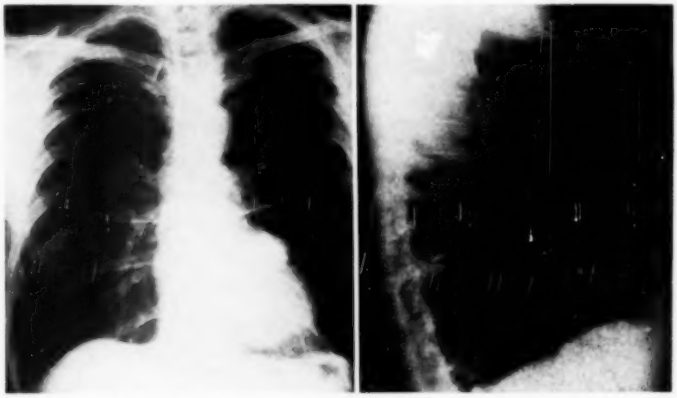


FIG. 7. Solitary tuberculoma of lower lobe of left lung. Resection of superior segment of left lower lobe of lung resulted in complete extirpation of the lesion: (A) (Left) PA view. (B) (Right) Lateral view.

In these patients, it is important that all normal pulmonary tissue be preserved, if possible. It has been pointed out that many such patients have superior segments of the lower lobes which are free of disease while all or some of the basal segments are involved in the disease process. In a much smaller percentage of patients, the basal segments are free of disease but the superior segments show bronchiectasis. Under such circumstances, the principles of segmental resection become of great importance and today they are widely practiced. Boiled down to a few words, these principles dictate the preservation of normal bronchopulmonary segments where possible in such instances of extensive, bilateral bronchiectasis.

It must be admitted that there are still certain disadvantages encountered in the application of the principles enumerated above. Chief of these is a higher incidence of bronchopleural fistula and postoperative empyema than is the case with lobectomy. In addition, some surgeons have found that a previously normal

superior segment of the lower lobes has become the site of bronchiectasis after segmental resection of diseased basal units of the lobe. This has been called traction bronchiectasis by some workers. Kergin (12) has revealed that this complication was of some moment in his patients and he has adopted a method of suturing the superior segment of the lower lobe to the adjoining segment of the upper lobe to prevent distortion and excessive traction upon this preserved segment during the process of re-expansion of the lung after surgery.

Additional instances in which segmental resection has met with wide application include certain types of solitary pulmonary cysts (figure 5); solitary metastases (figure 6); solitary tuberculomata (figure 7); quiescent, solitary pulmonary abscesses and in certain benign pulmonary neoplasms such as hamartomata and fibromata.

SUMMARY

1. Anatomical knowledge of the typical distribution of the pulmonary segments has been stabilized.

2. Atypical or anomalous patterns for the bronchopulmonary segments are continually under investigation and the findings are being placed in the literature and will continue to be so explored and reported.

3. A universally accepted and adopted system of nomenclature of the segments of the lungs is imperative. A plea has been made in behalf of the Jackson-Huber classification.

4. The surgical application of segmental pulmonary resection has been discussed briefly and its advantages and disadvantages have been enumerated.

SUMARIO

Importancia Quirúrgica de la Distribución Anatómica de los Segmentos Pulmonares

1. Nuestros conocimientos anatómicos de la distribución típica de los segmentos pulmonares han sido estabilizados.

2. Las formas atípicas o anómalas de los segmentos pulmonares se hallan continuamente en investigación, vertiéndose los hallazgos en la literatura, y continuarán siendo explorados y comunicados.

3 Un sistema de nomenclatura de los segmentos pulmonares, universalmente aceptado y adoptado, resulta imperativo. Abógase aquí por la adopción de la nomenclatura de Jackson-Huber.

4. Discútense sucintamente la aplicación quirúrgica de la resección segmentaria y sus indicaciones, limitaciones y complicaciones.

REFERENCES

(1) Boyden, E. A.: Intrahilar and related segmental anatomy of lung, Surgery, 1945, *18*, 706.

(2) Boyden, E. A., and Hartmann, J. F.: Analysis of variations in bronchopulmonary segments of left upper lobes of 50 lungs, Am. J. Anat., 1946, *79*, 321.

(3) Brock, R. C.: The Anatomy of the Bronchial Tree, Oxford Univ. Press, London, 1946.

(4) Churchill, E. D., and Belsey, R.: Segmental pneumonectomy in bronchiectasis; lingula segment of left upper lobe, Ann. Surg., 1939, *109*, 481.
(5) Foster-Carter, A. F.: Anatomy of bronchial tree, Brit. J. Tuberc., 1942, *36*, 19.
(6) Jackson, C. L., and Huber, J. F.: Correlated applied anatomy of bronchial tree and lungs with system of nomenclature, Dis. of Chest, 1943, *9*, 319.
(7) Scannell, J. G.: Study of variations of bronchopulmonary segments in left upper lobe, J. Thoracic Surg., 1947, *16*, 530.
(8) Scannell, J. G., and Boyden, E. A.: Study of variations of bronchopulmonary segments of right upper lobe, J. Thoracic Surg., 1948, *17*, 232.
(9) Scannell, J. G.: An anatomic approach to segmental resection, J. Thoracic Surg., 1949, *18*, 64.
(10) Blades, B.: Conservation of lung tissue by partial lobectomy, Ann. Surg., 1943, *118*, 353.
(11) Overholt, R. H., and Langer, L.: New technique for pulmonary segmental resection; its application in treatment of bronchiectasis, Surg., Gynec. & Obst., 1947, *84*, 257.
(12) Kergin, F. G.: The surgical treatment of bilateral bronchiectasis, J. Thoracic Surg., (in press).

Discussion of Symposium on Segmental Pulmonary Anatomy

Dr. Norman J. Wilson, Brookline, Massachusetts: It is a real privilege to be permitted to discuss these papers of Doctors Jackson and Kent and their associates which have served to crystallize our concepts concerning the surgical and pathological anatomy of the lung. I am sure that every thoracic surgeon feels deeply indebted to them.

I should like to re-emphasize the plea which Doctor Kent made for accepting the nomenclature as outlined by Jackson and Huber. It would seem to be very essential that we all accept this standard nomenclature so that in the future we shall all talk the same language when speaking of the bronchopulmonary segments.

The localization of pulmonary pathology according to the bronchopulmonary segment involved is especially important in bronchiectasis which is a purely segmental disease process. It is also essential prior to instituting collapse therapy in tuberculous patients. At times it is impossible after collapse has been instituted to localize the pathology with accuracy. In the future, it would be ideal if internists, roentgenologists, and surgeons alike were to use the bronchopulmonary segments in expressing the location of the pathology and if this concept were taught to the medical students and resident staffs now in training.

The advantages of segmental resection are conservation of lung tissue, less overdistention, and less distortion of the remaining segments. The disadvantages of segmental resection are: (*1*) The fact that, technically, it is a more difficult operation than lobectomy and most operators find a higher percentage of complications, especially early in their experience with the procedure. (*2*) Most pulmonary lesions during the acute or exudative phase cross the boundaries of the bronchopulmonary segment and do not lend themselves safely to segmental resection. At the recent meeting of the Association of Thoracic Surgeons, Dr. Robert Shaw of Dallas pointed out the increased morbidity associated with operating on lung abscesses during the acute or subacute phase as compared with the segmental resection of chronic lung abscesses or bronchiectasis. It would seem that this would also be true of tuberculosis in the exudative phase.

Segmental resection finds its greatest usefulness in the treatment of patients with bilateral bronchiectasis where the conservation of lung tissue is imperative. It also finds a place in the treatment of chronic lung abscess, benign tumors, cysts, and tuberculomata. It has been used successfully in combination with lobectomy in the treatment of pulmonary tuberculosis, especially where the preservation of the basal segments of the lower lobe is desirable because of poor respiratory reserve or because of a contralateral lesion of questionable stability. It also is a useful procedure in removing tumors of unknown type for frozen section. If the tumor proves to be benign, nothing else is necessary. If the tumor proves to be malignant, more radical resection is indicated.

The most important technical problem is to carry out the dissection in the proper plane. The work of Boyden and other anatomists first pointed out the significance of intersegmental veins. We have been deeply indebted on our service to Dr. Beatty Ramsay whose work pointed the way to finding safely the intersegmental plane and developed a technique for working in this plane without injuring adjacent segments. The intersegmental vein is the guide to the intersegmental plane and the important technical steps are to carry out the dissection on the side of the vein of the segment which is to be removed, and to keep the plane flattened so that the adjacent segment will not become tented and subjected to injury. Prior to using this technique, the incidence of empyema at the Overholt Thoracic Clinic fell between 20 per cent and 30 per cent. This technique was first used in September 1948 and between that date and February 1949, 28 consecutive segmental resections were performed without an empyema or a serious complication.

The advent of segmental resection has created new problems which must be solved. We must turn to the clinical physiologist for help because we must be able in the future to determine objectively just how much function we are saving in the various types and combinations of segmental resections. The question also often arises as to whether or not segmental resection is preferable to lobectomy in patients with unilobar bronchiectasis. Further clinical experience and physiological studies will be required before we can know the answers to many of these problems. It would seem that we should proceed with caution in applying segmental resection to disease processes of an inflammatory nature which cross the segmental planes, such as acute suppurative disease and tuberculosis. Because we can now remove a bronchopulmonary segment with technical finesse does not necessarily mean that this is the operation or procedure of choice. It must be kept in mind that, although segmental resection is effective in the treatment of certain pathological processes, it has the potentialities of a boomerang in treating others.

THE PHYSIOLOGICAL EFFECTS OF PNEUMOPERITONEUM UPON THE RESPIRATORY APPARATUS[1,2,3]

GEORGE W. WRIGHT, RONALD PLACE, AND FRANK PRINCI

(Received for publication May 4, 1949)

INTRODUCTION

The beneficial effects of pulmonary collapse have been variously explained by such factors as a diminution in pulmonary blood or lymph flow, a limitation of motion in the affected parts, stasis or hyperemia developing in the diseased tissues, and currently by a relaxation of the elastic forces present in the distended lung. Although certain of the above changes do develop in the collapsed lung, their true role has not been critically demonstrated and, in our opinion, the fundamental mechanism of the beneficial effects of collapse therapy remains an enigma. Even though acceptable proof of the modus operandi of collapse therapy is lacking, it is difficult to ignore the probable association between a reduction in lung size, which appears to be common to all forms of collapse therapy, and the favorable influence of this type of treatment. Moreover, a correlation between the degree of lung collapse and the effectiveness of treatment seems logical, although this also lacks critical confirmation.

The following study was undertaken in an effort to ascertain the quantitative aspect of variations in lung size consequent to pneumoperitoneum. In addition, observations concerning tidal air and minute ventilation under resting conditions were made before and after pneumoperitoneum in all cases, and in one a bronchospirometric study of the effect of pneumoperitoneum plus paralysis of the hemidiaphragm was carried out. In 10 cases, the effects of pneumoperitoneum upon the maximum breathing capacity were measured. The limited number of cases studied is regrettable, especially as to the effect of adding a paralysis of the hemidiaphragm to an established pneumoperitoneum and also as to the use of binders. Nevertheless, as the observations appear to be unique in the extant literature, and because it is not planned to pursue these investigations further in the immediate future, the limited data are published at this time.

METHODS

The degree to which the lung is distended at any moment is closely related to the volume of gas contained therein. Variations of distention can therefore be determined by measuring the volume of air present within the lungs at a given phase of respiration. Some

[1] From the Department of Physiology, Edward L. Trudeau Foundation, Saranac Lake, New York.

[2] Presented before the Medical Section, as part of the symposium on *Laboratory and Research*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 4, 1949.

[3] This study was made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, Medical Section of the National Tuberculosis Association.

consideration must be given to the fact that the volume of blood contained in the thorax will influence the gas content of the lung and is variable. If thoracic blood volume variations occur outside the pulmonary parenchyma proper, e.g. in the great vessels or heart, the consequent change of lung gas volume accurately represents a modification of the degree of lung distention. If, however, a variation of blood volume occurs within the parenchyma of the lung, the lung gas volume will show a concomitant change even though a modification of the degree of lung distention need not have occurred. Although a shift of blood from the abdomen and limbs into the thorax is believed to occur when the recumbent posture is assumed, there are no available data indicating the proportion which pools in the lung as opposed to the great vessels. The marked diminution in the size of the lung (during quiet breathing) that can be observed fluoroscopically to occur when the subject is changed from an erect to a recumbent position assures one that the difference in gas content of the lung measured in these two positions represents, in a large measure, a change in the degree to which the lung is distended. The elevation of intrapleural pressure known to occur when the body is shifted from the standing to the recumbent position is further evidence that this postural change reduces the degree to which the lung is distended. For present purposes and until knowledge to the contrary is presented, it appears reasonable to assume that a variation of the gas content of the lungs is indicative, though perhaps not a precise measurement, of a proportionate change in the degree of pulmonary distention.

In this communication, the volume of gas contained in the lungs at the end of a quiet expiration is termed the Functional Residual Air (FRA), at the end of a maximal expiratory effort, the Residual Air (RA), and at the end of a maximal inspiratory effort, the Total Volume (TV). The volume of gas expelled by a maximal forced expiration beginning at the mid position (end of quiet expiration) is termed Reserve Air (ReA) and is the same as the difference between the FRA and RA. The volume of gas inhaled by a maximal forced inspiration beginning at the mid position is termed Complementary Air (CA) and is the same as the difference between the TV and FRA. The complementary air added to the reserve air constitutes the Vital Capacity (VC).

The CA and ReA were determined by direct spirography. The FRA was determined by the method of Cournand, Baldwin, Darling, and Richards (1), using pure oxygen to rinse the nitrogen from the lungs. This method was modified (and will be described in detail in a subsequent publication) to permit the subject to record his CA and ReA with a spirometer and then receive oxygen through the open circuit, thus providing a correction for the FRA and allowing true duplicates of the entire pulmonary volumina. In the experience of the present investigators, the method of Cournand *et al.* has been entirely satisfactory, as it customarily provides duplicate determinations that are within a 3 per cent deviation from the mean.

The tidal air and minute ventilation were calculated from the spirometer tracings.

The Maximum Breathing Capacity (MBC) was determined by the method described by Hermanssen (5) using a specially constructed low-resistance valve and tubing (lumen 1.5 inches in diameter throughout) and expiring into a Douglas Bag. Collections of thirty seconds each were made, the volume being expressed in liters per minute (wet) at 37°C. Duplicates within 5 per cent of the mean were required.

Bronchospirometry in the single case was done as described previously (2).

MATERIAL AND MANNER OF STUDY

The pulmonary volumina were measured by suitable duplicates, with the subject in the standing position after being erect for twenty or more minutes, and with the subject in the recumbent position (head only elevated by a thin pillow) after lying quietly for a minimum of twenty minutes. Pre-pneumoperitoneum studies were made within a week prior to the induction of the pneumoperito-

neum. Measurements during pneumoperitoneum were made in all cases forty-eight hours after the last refill and the data published herein are of the determinations made when pneumoperitoneum was considered to be fully established. The intraperitoneal pressure was generally +6 to +8 cm. of H_2O in those cases evidencing a "good" elevation of the diaphragm and +12 to +18 cm. of H_2O in those evidencing a "limited rise" of the diaphragm. Refills were usually 600 to 900 cc. in volume every ten days to two weeks.

The MBC was measured on the same day as the lung volume studies. Bronchospirometry was carried out in the single case forty-eight hours after a refill both before and ten days after the hemidiaphragm was paralyzed.

Satisfactory studies were made in the erect and recumbent positions on 17 cases and in the recumbent position only on 2 additional cases. In some there was a pre-existing paralysis of the hemidiaphragm as indicated by an asterisk adjacent to the case number in table 2. In none was there evidence suggesting that there would be an impediment to the anticipated elevation of the diaphragm, except Case 19, in which severe pulmonary emphysema (RA = 57 per cent of TV) was known to be present, and Case 18, in which severe generalized pulmonary fibrosis with a small lung was associated with a diaphragm already somewhat elevated prior to the induction of pneumoperitoneum.

OBSERVATIONS

The lung volume, MBC, and bronchospirometry data of Case 17 are presented in figure 1 and table 1. This case portrays the effects of change of body posture and of pneumoperitoneum that were observed to be common for the series of cases. Of greatest interest is the effect of posture and pneumoperitoneum upon the FRA. The size or state of distention of the lung for virtually the entire twenty-four hours of each day is represented by the FRA with a cyclic increase superimposed by the tidal air. There are also intermittent variations of volume of a magnitude greater than the tidal air which occur during sighing, coughing, laughter, or severe physical exertion. It is unfortunate that for technical reasons the lungs are customarily roentgenographed in the position of full distention, because this rarely assumed position of the lung has thus become firmly fixed in the minds of physicians as portraying *the* physiological state of the lung. There would be greater clarity of thinking about the volumetric effects of collapse therapy if the fluoroscope rather than the conventional roentgenogram were more commonly used.

It has been shown previously that the gas content of the lungs is diminished by changing from the erect to the recumbent posture. The magnitude of this change as measured in Case 17 is indicated by comparing block A_1 with B_1 in figure 1, and for the series is shown in table 2, column A. The mean and extremes of the change in this series are virtually identical with those of a group of 20 normal males slightly older than were previously studied in this laboratory (3). It is apparent, therefore, that recumbency is of itself actually a true form of "collapse therapy."

The establishment of pneumoperitoneum markedly diminishes the FRA in the standing position. In some instances, it is as effective in this respect as is

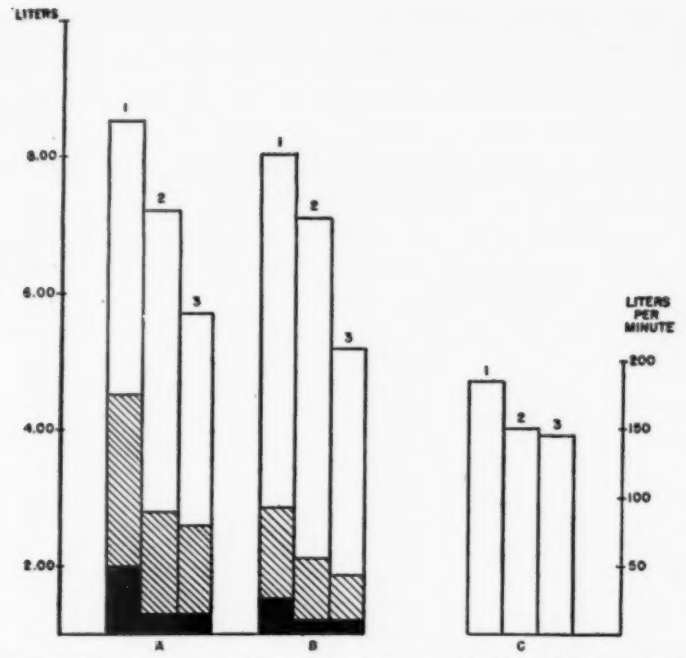


FIG. 1. The effect of pneumoperitoneum and of a combination of pneumoperitoneum plus paralysis of the hemidiaphragm upon the pulmonary volumina and Maximum Breathing Capacity of Case 17.

A—In the erect position

B—In the recumbent position

C—Maximum Breathing Capacity

1—Before pneumoperitoneum

2—During pneumoperitoneum

3—During pneumoperitoneum plus paralysis of the left hemidiaphragm.

In A and B, the solid block is the Residual Air, the cross-hatched block is the Reserve Air, and the clear block is the Complementary Air. The Functional Residual Air is made up of cross-hatched plus solid blocks, and the Total Volume by all three blocks.

TABLE 1

The Effect of Adding Paralysis of the Left Hemidiaphragm to a Pre-existing Pneumoperitoneum as Measured by Bronchospirometry

	PNEUMOPERITONEUM ALONE		PNEUMOPERITONEUM PLUS PARALYSIS OF THE LEFT HEMIDIAPHRAGM	
	Right	Left	Right	Left
	per cent		*per cent*	
M.V.	64	36	74	26
O_2 Cons.	72	28	80	20
CO_2 Output	67	33	78	22
V.C.	69	31	79	21

recumbency, a fact demonstrated by comparing A_2 with B_1 in figure 1. In others, it may be less effective or even more effective than recumbency alone, as shown by a comparison of columns B and A in table 2. For purposes of brevity, the complete data of the pulmonary volumina are not presented at this time. It can be

TABLE 2

The Effect of Pneumoperitoneum and Body Posture upon the Functional Residual Air and Maximum Breathing Capacity

CASE NUMBER	A	B	C	D	E
1	30	16	−24	42	−7
2	43	30	+10	37	
3	12	26	−30	39	−15
4*	34	43	−30	54	+4
5	44	29	−23	57	−10
6	38	49	−30	57	−13
7*	21	21	−12	30	
8	30	15	−9	36	−16
9	27	23	−27	46	−5
10	38	25	−16	48	
11	29	33	−30	51	
12	39	44	−33	59	−10
13	34	16	−13	43	
14	20	32	−26	41	
15*	28	39	−17	41	
16	40	33	0	40	+16
17	37	37	−24	52	−12
18			+6		
19			+13		−10
Mean	32	30		46	

A: Per cent by which the Functional Residual Air was diminished when the body was shifted from the standing to the recumbent position.

B: Per cent by which the Functional Residual Air, measured with the body in the standing position, was diminished by fully established pneumoperitoneum.

C: Per cent by which the Functional Residual Air, measured with the body in the recumbent position, was altered by a fully established pneumoperitoneum. The sign indicates the direction of the change.

D: Per cent by which the Functional Residual Air, measured with the body in the standing position and without pneumoperitoneum, was diminished by a well-established pneumoperitoneum and recumbent body posture combined.

E: Per cent by which the Maximum Breathing Capacity was altered by a fully established pneumoperitoneum.

* Pre-existing paralysis of the hemidiaphragm.

stated, however, that, in addition to its effect on the FRA, pneumoperitoneum also reduces the TV and RA in the erect position, although it has relatively little effect on the CA.

The FRA measured in the recumbent posture is still further diminished by the establishment of pneumoperitoneum, as demonstrated by comparing B_2 with B_1 in figure 1. This change occurred in 15 of the 19 cases studied, but in the other

4 there was either no further change or even a slight increase, as shown in column C, table 2. There was no apparent reason for the failure of pneumoperitoneum to cause a further diminution of the recumbent FRA in Case 16. Relatively little effect was anticipated in Case 19 because this subject has severe, diffuse, obstructive emphysema with a relaxed abdominal wall. Studies in this laboratory (3) have shown that persons with severe obstructive emphysema fail to show an appreciable reduction of the FRA upon changing from the erect to the recumbent position. The lungs simply fail to collapse, behaving under these circumstances in a manner similar to that which can be observed when the thoracic cage is opened at autopsy. As indicated in table 3, the use of a binder

TABLE 3

The Effect upon the Pulmonary Volumina of Applying an Abdominal Binder in the Presence of Pneumoperitoneum

	TOTAL VOLUME	VITAL CAPACITY	COMPLEMENTARY AIR	FUNCTIONAL RESIDUAL AIR	RESERVE AIR	RESIDUAL AIR
Case 2	*Liters*	*Liters*	*Liters*	*Liters*	*Liters*	*Liters*
Erect, without binder	2.95	2.08	1.61	1.34	0.47	0.87
Erect, with binder	2.69	1.76	1.57	1.12	0.19	0.93
Recumbent, without binder	2.87	1.91	1.67	1.20	0.24	0.96
Recumbent, with binder	2.50	1.57	1.38	1.12	0.19	0.93
Case 14						
Erect, without binder	2.45	1.72	1.37	1.08	0.35	0.73
Erect, with binder	2.30	1.46	1.22	1.08	0.24	0.84
Recumbent, without binder	2.20	1.35	1.25	0.95	0.10	0.85
Recumbent, with binder	1.99	1.05	1.02	0.97	0.02	0.95
Case 19						
Erect, without binder	—	—	—	—	—	—
Erect, with binder	—	—	—	—	—	—
Recumbent, without binder	6.85	3.12	2.15	4.70	0.97	3.73
Recumbent, with binder	5.04	2.50	1.82	3.22	0.68	2.54

partially remedied this lack of pneumoperitoneum effect upon the FRA in Case 19. The failure to diminish the recumbent FRA in Case 18, in spite of an intra-abdominal pressure of 20 cm. of H_2O, is not clear. This patient had a very extensive fibrosis diffusely distributed throughout both lungs which was apparently the residuum of extensive tuberculosis. There was no clear evidence of severe obstructive emphysema and the MBC and the RA expressed as a per cent of TV were only slightly abnormal. The diaphragm was elevated and moderately limited in mobility. Some obscure factor prevented the anticipated further elevation of the diaphragm. The failure to establish a further diminution of the recumbent FRA in Case 2 appeared related to the fact that the anterior abdominal wall was very flabby and lacking in tone as a result of multiple pregnancies. The patient would not wear a binder or tolerate high pressures.

In the recumbent position, pneumoperitoneum reduced the TV and also the RA but had only a slight effect upon the CA. The marked change in lung size that resulted from a combination of recumbency and pneumoperitoneum is ap-

parent in the contrast of B_2 and A_1 in figure 1 and by inspection of column D in table 2. This comparison reveals the most impressive effect of pneumoperitoneum upon the pulmonary volumina.

The effects of paralysis of the hemidiaphragm added to an established pneumoperitoneum were observed in Case 17 and are shown in figure 1, A_3 and B_3, and in table 1. The RA was not appreciably altered in either the erect or recumbent posture. The FRA was measurably, though not strikingly, diminished in both positions. The most marked change occurred in the CA which was reduced by 1.49 liters in the standing position and 1.76 liters in the recumbent position. Bronchospirometric studies made before and after the addition of a left hemidiaphragm paralysis in Case 17 are shown in table 1. Although the extent to which the left lung participates in each breath is measurably reduced by the paralysis, the ribs are apparently still an effective means of bringing about a cyclic distention of the left lung. The effects of paralysis of the hemidiaphragm upon the pulmonary volumina and the dynamics of respiration appear to be the same in this case with a pneumoperitoneum as when the paralysis is induced in the absence of pneumoperitoneum. The size of the lungs *at the end of quiet expiration* is little if at all affected by the paralysis, but the lung on the paralyzed side is distended to a lesser extent with each ordinary breath and is further protected, although not entirely so, from periodic distention by deep breaths. The effects of pneumoperitoneum and paralysis of the hemidiaphragm in this single case (supported by fluoroscopic and roentgenographic confirmation in this and other cases) were additive.

The effect of applying a tight abdominal binder to an established pneumoperitoneum was studied in Cases 2, 14, and 19. The data are shown in table 3. There was relatively little further change in the pulmonary volumina of Cases 2 and 14, but quite a large change in all divisions of the volumina was observed in Case 19. As noted earlier, pneumoperitoneum alone produced virtually no change in the lung size of Case 19. Since the diaphragm was low even in the presence of the pneumoperitoneum, the tightly applied binder had an opportunity to bring about an elevation of the diaphragm and thus effect a diminution of the pulmonary volumina. In Case 14, and to a lesser extent in Case 2, the diaphragm was already elevated as a result of the pneumoperitoneum plus the recumbent position, and a binder had little chance to force the diaphragm to a further elevation.

The effect of pneumoperitoneum on the MBC is shown in table 2. In general, the reduction is relatively slight. This finding is readily explainable in view of the fact that a loss of stroke volume can be compensated for over a quite wide range by an increase of the number of breaths made in the 30 seconds allotted for the test (made possible because each stroke is smaller). These results confirm the data of Steinlin (4) who also observed only a slight reduction of the MBC in pneumoperitoneum.

The tidal air and minute ventilation measured at rest were not appreciably changed by the establishment of pneumoperitoneum. Minor variations were noted but were inconstant and thought to be within the range of variations for untrained subjects.

COMMENT

Pneumoperitoneum, if fully established, is an effective method of reducing the size or state of distention of the lung. In this respect, it is more adequate than paralysis of the hemidiaphragm. Since the modern concept of the degree of collapse desired in intrapleural pneumothorax commonly makes use of less than a 50 per cent collapse of the lung, pneumoperitoneum plus recumbency is just as effective in collapsing the lung as is pneumothorax, unless virtually complete collapse of the lung is desired.

The addition of a paralysis of the hemidiaphragm to an established pneumoperitoneum in the single case studied affected the FRA only slightly, but did reduce the cyclic distention of the homolateral lung caused by quiet respiration and partially protected it against periodic deep breaths. This finding should in no way be construed to invalidate the use of hemidiaphragm paralysis in combination with pneumoperitoneum. It should indicate clearly, however, the need for more study of this combination of therapeutic methods, and seriously raises a question about their routine simultaneous use.

The application of an abdominal binder as an adjunct to pneumoperitoneum deserves further study. If the lungs are already reduced in volume and the diaphragm has ascended in the thorax to the limit imposed by factors intrinsic in the muscle itself, little seems likely to be further accomplished by a binder. If, however, the lung has not been appreciably reduced in volume because of intrinsic pulmonary factors or a lax abdominal wall, a binder might be of considerable aid in further collapsing the lung.

That pneumoperitoneum affects both lungs equally seems apparent from inspection of the roentgenograms taken at various phases of breathing. Actual measurements of the roentgenographic changes in this series of patients may be published at a later date. It is possible, but as yet unproved, that the addition of a paralysis of the hemidiaphragm may selectively reduce the size of the homolateral lung in comparison to its contralateral mate. Inspection of the roentgenograms taken at the end of quiet expiration in the recumbent position shows little evidence of such a selective change.

Since the pulmonary volumina of the erect person with a pneumoperitoneum closely simulate those of a recumbent person without pneumoperitoneum, it is tempting to think that pneumoperitoneum might be used as a substitute for recumbency when the latter is not feasible. The enhanced effect of the reduction of lung size when recumbency is added to pneumoperitoneum indicates the advantages of recumbency when feasible.

The relatively slight reduction of MBC that results from pneumoperitoneum, together with the fact that it is a reversible form of treatment, makes it possible to use this form of collapse therapy in cases of severe respiratory crippling.

SUMMARY

Pneumoperitoneum causes a marked reduction in the functional residual air, residual air, and total volume of a subject in the erect position. A similar though quantitatively less marked effect is observed when the subject is studied in the recumbent position.

The effects upon the pulmonary volumina and proportion of respiration performed by each lung (bronchospirometry), produced by adding a paralysis of the hemidiaphragm to a pre-existing pneumoperitoneum, were observed. A small further reduction of functional residual air and a large reduction of complementary air, together with a reduction in function by the homolateral lung, resulted from the added paralysis.

An abdominal binder caused a slight diminution of pulmonary volumina in two cases and a marked diminution in a third case when applied in the presence of pneumoperitoneum.

The maximum breathing capacity was only slightly reduced by the induction of pneumoperitoneum.

SUMARIO

Efectos Fisiológicos del Neumoperitoneo sobre el Aparato Respiratorio

El neumoperitoneo provoca marcada disminución del aire residual funcional, el aire residual y el volumen total en un sujeto en posición erecta. Obsérvase un efecto semejante, pero cuantitativamente menos pronunciado, cuando se estudia al sujeto, recostado.

Estudióse también el efecto sobre los volúmenes pulmonares y la proporción de respiración ejecutada por cada pulmón (broncoespirometría), producido al sobreponer una parálisis del hemidiafragma a un neumoperitoneo preexistente. La parálisis sobrepuesta agregó una pequeña reducción del aire residual funcional y una gran reducción del aire complementario, junto con una disminución de la función del pulmón homolateral.

Una faja abdominal ocasionó una leve disminución de los volúmenes pulmonares en dos casos y una pronunciada disminución en otro caso, cuando se aplicó en presencia de un neumoperitoneo.

La capacidad respiratoria máxima apenas descendió por virtud de la inducción del neumoperitoneo.

Acknowledgment

The excellent cooperation of the patients who volunteered for this study is deeply appreciated. We are grateful also to the physicians of the Trudeau Sanatorium staff, especially Dr. Roger S. Mitchell, for their invaluable aid in making these observations.

REFERENCES

(1) Cournand, A., Baldwin, E. D., Darling, R. C., and Richards, D. W., Jr.: Studies on intrapulmonary mixture of gases: IV. The significance of the pulmonary emptying rate and a simplified open circuit measurement of residual air, J. Clin. Investigation, 1941, *20*, 681.

(2) Wright, G. W., and Woodruff, W. W.: Bronchospirography: Ventilation and oxygen absorption of normal and diseased lungs during nitrogen respiration in the opposite lung, J. Thoracic Surg., 1942, *11*, 278.

(3) Wright, G. W.: Unpublished data.

(4) Steinlin, H.: Atemfunktionsprüfung bei temporärer Phrenikusausschaltung verbunden mit Pneumoperitoneum, Schweiz. Ztschr. Tuberk., 1946, *31*, 34.

(5) Hermannsen, J.: Untersuchungen über die maximal ventilationsgrosse (Atemgrenzwert), Ztschr. f. d. ges. exper. Med., 1933, *90*, 130.

EVALUATION OF STREPTOMYCIN REGIMENS IN THE TREATMENT OF TUBERCULOSIS[1,2,3,4]

An Account of the Study of the Veterans Administration, Army, and Navy, July 1946 to April 1949

WILLIAM B. TUCKER

(Received for publication August 22, 1949)

INTRODUCTION

The cooperative investigation of the effect of streptomycin in the treatment of tuberculosis by the Veterans Administration, Army, and Navy began in July 1946. The cooperating investigators have abided by common protocols mutually agreed upon, governing indications for treatment, observations of results, and methods of reporting results (1). Beginning with the study of pulmonary tuberculosis, the investigation was gradually extended until, at the end of its first year, all types of tuberculosis were included in its range. Comprehensive progress reports of the study have appeared on two occasions (2, 3).

The general objective of the study has been to determine the efficacy and the limitations of streptomycin in the treatment of tuberculosis. Originally, relatively high daily doses, 1.8 or 2.0 Gm., were employed for 120 days. This stage of the investigation confirmed the observation that streptomycin exerts a favorable effect on the course of tuberculosis in man (1). In subsequent stages of the investigation variations of the original regimen have been explored, such as: lower daily dosages, shorter periods of administration, and reduction in the number of daily injections into which the total daily dose is divided. To date, streptomycin therapy has been completed in approximately 4,500 cases, exclusive of courses of treatment given for relatively short periods of time before and after certain surgical procedures. Approximately 2,000 cases of pulmonary tuberculosis have been treated.

The purpose of this paper is to summarize certain aspects of this cooperative investigation since its inception, particularly with reference to the effect that variations in streptomycin regimen have had upon toxicity, the emergence of streptomycin-resistant strains of *M. tuberculosis*, and suitable clinical observations. Primary emphasis will be placed upon the results of streptomycin treatment of pulmonary tuberculosis.

[1] From the Tuberculosis Service, Veterans Administration Hospital, Minneapolis, Minnesota, and the Department of Medicine, University of Minnesota.

[2] Presented before the Medical Section, as part of the symposium on *Streptomycin and Tuberculosis*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 3, 1949.

[3] Presented in part before the Seventh Streptomycin Conference, Veterans Administration, Denver, Colorado, April 22, 1949.

[4] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

METHODS

Administrative control: Original plans for the investigation were formulated by representatives of the Veterans Administration, Army, and Navy in May 1946, with the advice of representatives of the Public Health Service, the National Research Council, and the National Tuberculosis Association (1). Continuity has been provided through a Streptomycin Committee of the Central Office, Veterans Administration. As the study has progressed, committees from among the investigators and the consultants to the study have been appointed by the Streptomycin Committee, and since 1947 all decisions as to the course of the investigation have been the result of committee recommendations which were approved by the cooperating investigators. The Streptomycin Committee has continued to be responsible for administration of the program in the intervals between semiannual Conferences which were held for the evaluation of results and for planning the future course of the study.

Liaison between study units: Representatives of the Streptomycin Committee have visited all or most of the cooperating Study Units. Study Units have submitted monthly progress reports of their experience (bi-monthly since April 1948) which have been mimeographed and distributed to cooperating investigators. Streptomycin Conferences, of which there have been seven, have been held at intervals of approximately six months, to which all participating investigators, as well as consultants and other individuals interested, have been invited. In this manner there has been assured a considerable uniformity in the type of case treated, in the conditions of treatment, and in the observation and recording of results.

Introduction of variations of streptomycin regimen:

1. July 1946: 1.8 Gm. a day (0.3 Gm. every 4 hours), later 2.0 Gm. (0.4 Gm. every 4 hours 8 a.m. to midnight), for 120 days, employed in seven Study Units, increased to twenty-one Study Units in December 1946, all forms of tuberculosis.
2. May 1947: 2.0 Gm. a day (0.4 Gm. every 4 hours 8 a.m. to midnight), for 60 days, in seven Study Units, pulmonary tuberculosis only.
3. May 1947: 1.0 Gm. a day (0.2 Gm. every 4 hours 8 a.m. to midnight), for 120 days, in seven Study Units, all forms of tuberculosis.
4. May 1947: 1.0 Gm. a day (0.5 Gm. every 12 hours) for 120 days, in seven Study Units, all forms of tuberculosis.
5. October 1947: 0.5 Gm. a day (0.25 Gm. every 12 hours) for 120 days, in seven Study Units, pulmonary and laryngeal tuberculosis, and draining tuberculous sinuses only.
6. April 1948: 1.0 Gm. a day (0.5 Gm. every 12 hours, changed to 1.0 Gm. in a single dose daily in October 1948) for 42 days, all Study Units, all forms of tuberculosis.
7. April 1948: 0.5 Gm. a day (0.25 Gm. every 12 hours, changed to 0.5 Gm. in a single dose daily in October 1948) for 42 days, in the majority of forty-eight Study Units, nearly all forms of tuberculosis.
8. April 1948: 0.2 Gm. a day (in a single injection) for 120 days, and for 42 days, in six Study Units, tuberculous draining sinuses only.
9. October 1948: 1.0 Gm. a day (in a single injection) (2.0 Gm. a day in a single Study Unit) every third day for 120 days, eight Study Units, pulmonary tuberculosis only.
10. December 1948: 2.0 Gm. a day of *dihydrostreptomycin* (1.0 Gm. every 12 hours) for 42 days, all Study Units, all forms of tuberculosis.
11. Variations have been permitted in the treatment of miliary and meningeal tuberculosis, but the majority of these cases have been treated with 2.0 Gm. a day for 120 days or longer.

Random selection of cases on different streptomycin regimens: It was the original decision of the Streptomycin Committee to have the Study Units select suitable cases and then divide them at random into two groups, the one to be treated with streptomycin, the other to serve as controls. Adequate clinical material was not found to be available, and this plan was abandoned (1). The investigation of the original streptomycin regimen, 1.8 Gm. a day (later 2.0 Gm. a day) for 120 days provided no "controls" in the strict sense of comparing

treated cases with untreated cases. Beginning in May 1947, three regimens were investigated simultaneously, although each regimen was employed in only one Study Unit. Since April 1948, there has been alternation of cases in most Study Units according to a statistically satisfactory method of random selection.

Methods of reporting results: In the early stages of the study, results reported by investigators were pooled and compiled at the Streptomycin Conferences and reported in the *Minutes* of the first three Conferences. For the Fourth Conference (St. Louis, October 9–12, 1947) (4) a beginning was made in the assembling of data in tabular form. For subsequent Conferences pertinent data have been assembled from the Study Units in advance of the meetings and collected by the Streptomycin Committee for distribution to members of the Conferences (5, 6, 7). These compilations have been in summary tabular form, permitting relatively little cross-tabulation of the effect of various variables, but for the Seventh Conference (Denver, April 21–24, 1949) (7) data on cases of pulmonary tuberculosis were assembled on simplified individual case report forms, permitting the reporting of a number of pertinent cross-tabulations. Since February 1948, a committee appointed by the Streptomycin Committee has been in the process of developing individual case report forms for the major portion of cases treated. The first of these forms, for pulmonary tuberculosis and for miliary tuberculosis and tuberculous meningitis, were distributed in May 1949. Results so reported are to be analyzed and processed with the assistance of the Medical Research Statistics Division, Central Office, Veterans Administration, permitting a range of interpretation considerably wider than that which has been possible thus far. Results presented in this paper are derived almost entirely from data reported to the last three Conferences (5, 6, 7).

Reporting of change in tuberculous condition treated: In the absence of more objective criteria, investigators have been asked to report the results of streptomycin therapy not only in such terms as "improved" (and "healed" according to stipulated criteria), "unchanged", and "worse", but in different degrees of improvement and worsening. A "scale" which has been found to be practicable and to have a considerable degree of consistency of result has now been adopted. In employing the scale, investigators are requested to make every effort to assign uniform weighting to each point on the scale. The scale, which will also be employed in the individual case report forms, is as follows:

1. marked improvement
2. moderate improvement
3. slight improvement
4. no change
5. slight worsening
6. moderate worsening
7. marked worsening

For the Fifth Streptomycin Conference (5), changes were reported on a nine-point scale, which included extremes of very marked improvement and very marked worsening, but the simpler seven-point scale has now been adopted.

"Jury" reviews: Desiring to increase the objectivity of the observation of results, on two occasions investigators have been requested by the Streptomycin Committee to submit roentgenograms of treated cases of pulmonary tuberculosis to an impartial "jury" of experts for re-evaluation. The results of these two reviews have been reported (1, 5).

Statistical interpretations: The nature of the data and of the method of reporting has not permitted elaborate statistical analysis of results. It has not been possible to employ means, standard deviations, tests for the significance of the difference of means, or the analysis of variance. Reporting of results in terms of percentage of total samples has, however, permitted the use of the chi-square test, and this test has been employed in this paper where the data have been regarded as suitable. Where statements are made as to the "significance" of differences noted, it is understood that the probability of the difference being due to chance, as determined by the chi-square test, is less than 0.05 (less than one chance in twenty).

OBSERVATIONS

Toxicity

It is now well known that the course of the Good Ship Streptomycin lies between the Scylla of toxicity and the Charybdis of bacterial resistance. Fortunately both of these navigational hazards have now been well charted.

In figures 1, 2, and 3 may be seen the incidence of the more important toxic manifestations present among patients treated on seven different streptomycin regimens. In figure 1 the differences for the incidence of vertigo are significant among the cases treated on the first five streptomycin regimens: 2.0 Gm. a day

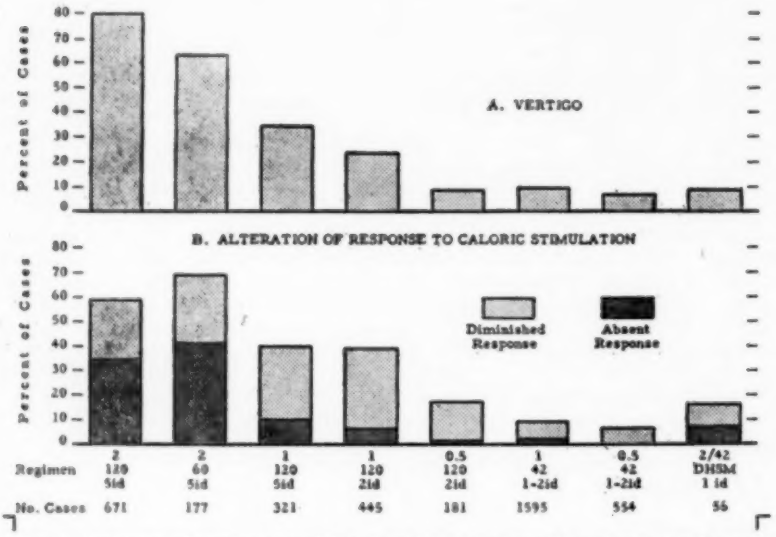


FIG. 1. Incidence of vestibular toxicity on various streptomycin regimens (during treatment period).

for 120 days[6], 2.0 Gm. a day for 60 days, 1.0 Gm. a day for 120 days (with both 5 and 2 injections a day), and 0.5 Gm. a day for 120 days. The differences are not significant among the cases treated on the following regimens: 0.5 Gm. a day for 120 days, 1.0 Gm. a day for 42 days, and 0.5 Gm. a day for 42 days. Much the same differences are noted in figure 1 for altered response, both diminished and absent, to caloric stimulation (by the modified Kobrak technique), except that the differences between the two 1.0 Gm. a day for 120-day regimens are not significant. These figures clearly establish that, as the daily dose of streptomycin is reduced from 2.0 to 1.0 to 0.5 Gm. a day, with duration constant at 120 days,

[6] Hereafter the regimen so designated will also be understood to include cases treated with 1.8 Gm. a day for 120 days.

there is significantly less vestibular toxicity; that, as duration of streptomycin therapy is shortened from 120 to 60 or 42 days there is less vestibular toxicity, although this decrease is less than in the case of reduction in the daily dose; and that, in the case of vertigo, reducing the number of injections of streptomycin per day, without otherwise altering the 1.0 Gm. a day for 120-day regimen, decreases toxicity somewhat.

In figure 2 may be seen the data for the incidence of certain mainfestations of renal toxicity. Differences reported in diminished renal function are not significant among cases treated on the four regimens of higher total dosage nor among those treated on the three of smaller total dosage, but on the three latter (those

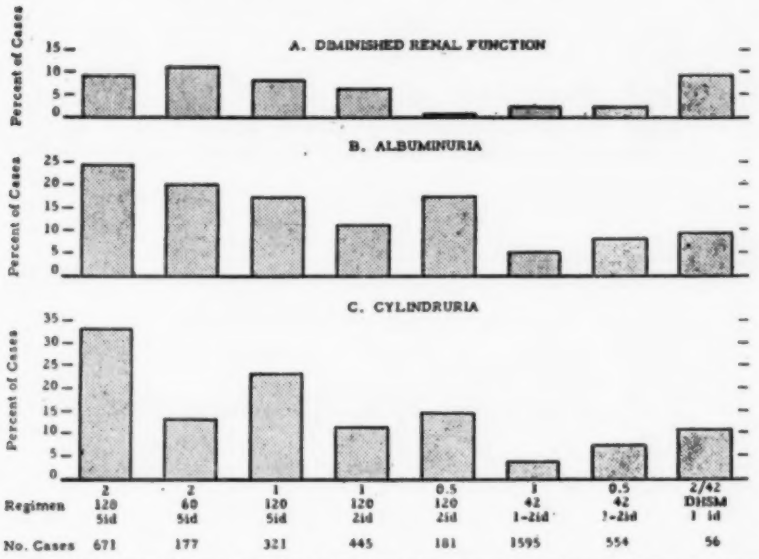


FIG. 2. Incidence of renal toxicity on various streptomycin regimens (during treatment period).

of 0.5 Gm. a day for 120 days, and 1.0 Gm. or 0.5 Gm. a day for 42 days) there is significantly less interference with renal function than among patients treated on the first four regimens. With respect to albuminuria and cylindruria, the data in figure 2 suggest that streptomycin regimens of longer duration are more often associated with a high incidence of toxicity than are those with larger daily dosages. The effect of reducing streptomycin dosage, through reduction in daily dosage, or duration, or number of daily injections, is less in the case of renal toxicity than in the case of vestibular toxicity.

The incidence of dermatitis, both mild and severe (figure 3), associated with streptomycin therapy, appears to be more related to duration of therapy than to daily dosage. Dermatitis is found to be present with significantly greater fre-

quency among patients treated on regimens of longer duration (120 days) than in patients treated for a shorter period (60 or 42 days), whether the daily dose is 2.0 Gm., 1.0 Gm. or 0.5 Gm. With respect to drug pyrexia (figure 3), there is significantly greater toxicity only in the case of the patients treated on the first regimen, that of 2.0 Gm. a day for 120 days.

In figure 3 are also presented the data for the frequency with which serious toxicity makes it necessary to terminate streptomycin therapy. There is found to be a significantly more frequent occurrence of this development between the two 2.0 Gm. a day regimens and the other five, and between the 1.0 Gm. a day for 120-day regimen in 5 divided doses and the remaining four.

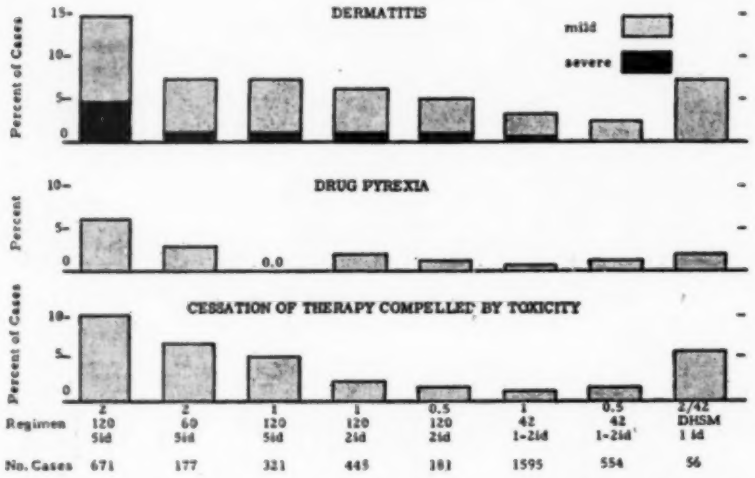


FIG. 3. Incidence of other toxicity on various streptomycin regimens (during treatment period).

The data presented in figures 1, 2, and 3 are summarized in table 1 which also includes the respective incidences of other toxic manifestations which are of lesser frequency and importance. From this evaluation it may be stated that, in general, there has been a reduction of streptomycin toxicity with the following modifications of streptomycin regimens, listed in the order of their importance: (*a*) reduction in daily dosage; (*b*) reduction in duration of therapy; and (*c*) decrease in the number of daily injections into which the total daily dose is divided. The effect of each of these variables has differed with the particular toxic manifestation studied.

The data for these toxic manifestations are based upon observations during the treatment period. Follow-up data on some of the manifestations have been reported to the last three Streptomycin Conferences (5, 6, 7). These data indicate that, whereas there is little change six months or more after the end of treatment

TABLE 1

Incidence of Toxicity to Streptomycin on Various Regimens

Regimes	*SM* 2 Gm. 120 days 5 i.d.		*SM* 2 Gm. 60 days 5 i.d.		*SM* 1 Gm. 120 days 5 i.d.		*SM* 1 Gm. 120 days 2 i.d.		*SM* 0.5 Gm. 120 days 2 i.d.		*SM* 1 Gm. 42 days 1–2 i.d.		*SM* 0.5 Gm. 42 days 1–2 i.d.		*DHSM* 2 Gm. 42 days 2 i.d.	
No. Patients Treated (Source of Data)	671 (5*)		177 (5*)		321 (5*)		445 (5*)		181 (6*)		1,595 (7*)		354 (7*)		56 (7*)	
Toxic Manifestation	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1. Toxicity Caused																
a. Cessation therapy	67	9.9	11	6.4	16	5.0	9	2.0	3	1.7	19	1.2	8	1.4	3	5.4
b. Interruption therapy	32	4.8	6	3.4	10	3.1	9	2.0	2	1.1	13	0.8	7	1.3	2	3.6
2. Vestibular																
a. Vertigo	537	80.0	111	62.7	110	34.3	103	23.1	16	8.8	151	9.8	40	7.2	5	8.9
b. Ataxia	302	45.0	46	26.0	66	20.6	51	11.5	7	3.9	40	5.4	13	4.0	7	17.5
(ataxia tested)	(**)		(**)		(**)		(**)		(**)		(737)		(323)		(40)	
c. c.s.r.§ dimin.	170	25.3	49	27.7	96	30.0	105	23.4	29	16.0	66	7.0	23	6.1	4	9.1
d. c.s.r. absent	229	34.1	73	41.2	33	10.3	24	5.4	2	1.1	15	1.6	1	0.2	3	6.8
e. c.s.r. altered	399	59.4	122	68.9	129	40.3	129	28.8	31	17.1	81	8.6	24	6.3	7	15.9
(c.s. tested)	(**)		(**)		(**)		(**)		(**)		(938)		(377)		(44)	
3. Auditory Loss																
a. to spoken voice	18	2.7	1	0.6	1	0.3	1	0.2	0	0.0	7	0.4	1	0.2	2	4.5
b. audiom., high range	61	9.1	26	14.7	9	2.8	31	7.0	2	1.1	57	5.4	26	6.2	2	4.5
c. audiom., low range (tested by audiom.)	32	4.7	8	4.5	4	1.2	11	2.5	0	0.0	11	1.0	9	2.1	2	4.5
	(**)		(**)		(**)		(**)		(**)		(1,059)		(419)		(44)	
4. Renal Function																
a. dimin., intermittent	43	6.4	6	3.4	24	7.5	19	4.3	9	0.0	25	1.6	8	1.4	1	1.8
b. dimin., maintained	19	2.8	13	7.4	1	0.3	7	1.5	1	0.6	12	0.8	4	0.7	4	7.1
c. dimin., int. and maint.	62	9.2	19	10.8	25	7.8	26	5.8	1	0.6	37	2.4	12	2.1	5	8.9
d. cylindruria	223	33.2	23	13.0	74	23.1	48	10.8	26	14.4	53	3.3	38	7.0	6	10.7
e. albuminuria	164	24.4	34	19.8	55	17.1	49	11.0	31	17.1	81	5.1	44	8.1	5	8.9
f. hematuria	54	8.0	23	13.0	9	2.8	12	2.7	21	11.6	28	1.8	16	2.9	2	3.6
5. Dermatitis																
a. mild	67	10.0	10	5.6	18	5.6	21	4.7	7	3.9	44	2.8	12	2.2	4	7.1
b. severe	31	4.6	2	1.1	4	1.2	5	1.1	2	1.1	8	0.5	0	0.0	0	0.0
c. all	98	14.6	12	6.7	22	6.8	26	5.8	9	5.0	52	3.3	12	2.2	4	7.1
6. Other																
a. eosinophilia (>6%)	426	63.5	87	49.2	118	36.8	154	34.6	60	33.1	206	12.9	82	14.8	15	26.8
b. blood dyscrasia	4	0.6	4	2.3	3	0.9	3	0.7	0	0.0	3	0.2	1	0.2	1	1.8
c. paresthesia	120	17.9	4	2.3	13	4.1	16	3.6	6	3.3	25	1.6	5	0.9	7	12.5
d. nausea and vomiting	111	16.5	7	7.9	9	2.8	22	4.9	3	1.7	26	1.6	12	2.2	6	10.7
e. fever	38	5.7	5	2.8	0	0.0	8	1.8	2	1.1	6	0.4	6	1.1	1	1.8
f. psychosis	14	2.1	1	0.6	5	1.6	1	0.2	0	0.0	3	0.2	0	0.0	0	0.0

* Identifies number of Streptomycin Conference from Minutes of which data are obtained.

** Information not available.

§ c.s.r. = caloric stimulation response.

SM = streptomycin.

DHSM = dihydrostreptomycin.

in diminution of response to caloric stimulation, or in ataxia, the incidence of subjective vertigo is generally less than half that present during treatment. Follow-up data with respect to auditory function six months or more after the end of therapy indicate that slightly less disability is present, audiometrically and to the spoken voice. Late increase in the incidence of these toxic manifestations has not been observed in this study.

Dihydrostreptomycin: Dihydrostreptomycin, in doses of 2.0 Gm. a day for 42 days, has been employed by the Study only for the past four months. At the Seventh Streptomycin Conference, toxicity data were reported for this hydrogenated product of streptomycin on the basis of 56 cases. The results are reported in figures 1, 2, and 3 and in table 1.

The more important toxic manifestations are summarized in table 2. In this table, by comparing the toxic manifestation of dihydrostreptomycin on a regimen of 2.0 Gm. a day for 42 days, in the middle column, with that of streptomycin on

TABLE 2

Comparison of Toxicity of Streptomycin and Dihydrostreptomycin

*Drug** / *Regimen†* / *Number of Cases*	*SM* 2/60 177	*DHSM* 2/42 56	*SM* 1/42 1,595
Toxic Manifestation	(Per cent of Cases)		
Vertigo	62.7‡	8.9§	9.8
Altered response to caloric stimulation	68.9‡	15.9‡	8.6
Dimin. renal function	10.8§	8.9‡	2.4
Dermatitis	6.7§	7.1‡	3.3
Cessation of therapy compelled by toxicity	6.4§	5.4‡	1.2

* SM = streptomycin, DHSM = dihydrostreptomycin.

† Numerator of fraction designates daily dose in grams, denominator duration of treatment in days.

‡ Difference between adjacent pairs statistically significant.

§ Difference between adjacent pairs not statistically significant.

a regimen of 2.0 Gm. a day for 60 days, to the left, it is possible to approximate a dose-for-dose comparison of the two drugs. A similar comparison based on identical periods of therapy may also be made by comparing the incidence of toxicity on a streptomycin regimen of 1.0 Gm. a day for 42 days with a 42-day dihydrostreptomycin regimen of 2.0 Gm. daily.

As the symbols for the statistical significances of the differences indicate in table 2, with dihydrostreptomycin there appears to be definitely less vestibular toxicity than with streptomycin, but no less impairment of renal function, dermatitis, or frequency with which toxicity causes cessation of therapy, when the two drugs are compared dose for dose. When streptomycin and dihydrostreptomycin regimens of the same duration are compared, 2.0 Gm. a day of dihydrostreptomycin is found to be associated with significantly more toxicity than 1.0 Gm. a day of streptomycin, except that the reported incidence of vertigo is not significantly different. These preliminary data therefore suggest that dihydrostrepto-

mycin is less toxic with respect to vestibular function, but not less toxic than streptomycin with respect to the other toxic manifestations mentioned. The number of cases treated with dihydrostreptomycin is small and it is anticipated that data reported to the next Streptomycin Conference will clarify the picture of the relative toxicities of the two related antibiotics.

Sensitivity of Tubercle Bacilli to Streptomycin

Throughout the streptomycin investigation, emphasis has been placed on determinations of sensitivity of tubercle bacilli recovered from patients before, during, and after completion of streptomycin therapy. Determinations were made at first in liquid media, more recently on solid media. Good comparability

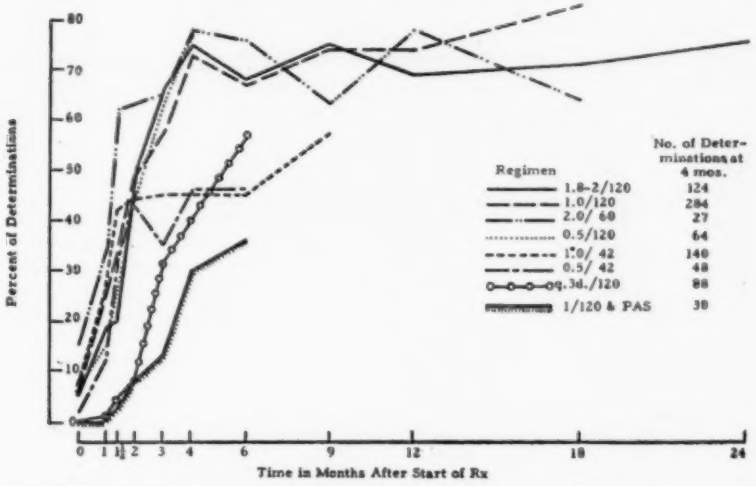


FIG. 4. Percentage of organisms resistant to 10 γ of streptomycin per ml. or more on various streptomycin regimens, at different times after start of therapy.

of results was found, and the results for the two methods combined are presented in figure 4, in the case of tubercle bacilli which proved to be resistant to 10 γ or more of streptomycin per ml.

Differences for the three 120-day regimens (2.0 Gm., 1.0 Gm., and 0.5 Gm. of streptomycin daily) of daily administration are not statistically significant; nor do significant differences exist between these data and those obtained from the 2.0 Gm. a day for 60-day regimen. Differences likewise are not significant between the two 42-day regimens. As a consequence, the percentages of resistant organisms for regimens of identical duration have been combined and are presented in figure 5.

Disregarding the daily dosage of streptomycin, it appears that there is definitely less emergence of resistant tubercle bacilli on a regimen of 42 days than on

regimens of either 60 or 120 days. The cumulative rates for the emergence of tubercle bacilli resistant to 10 γ per ml. or more when streptomycin was administered daily appear to be: first month, 20 per cent; second month, 50 per cent; third and fourth months, 62.5 and 75 per cent, respectively. Interpolations for regimens of other duration may be made between these points with a fair degree of accuracy.

Data have also been gathered for the percentage of organisms resistant to 100 γ of streptomycin per ml. or more. Figure 6 presents these data for approximately 500 cases treated on the 120-day regimens, in comparison with the resistance data for the 10 γ per ml. level. As may be seen, there is a fairly close parallel between the two rates, although they are at two levels, significantly different from each other.

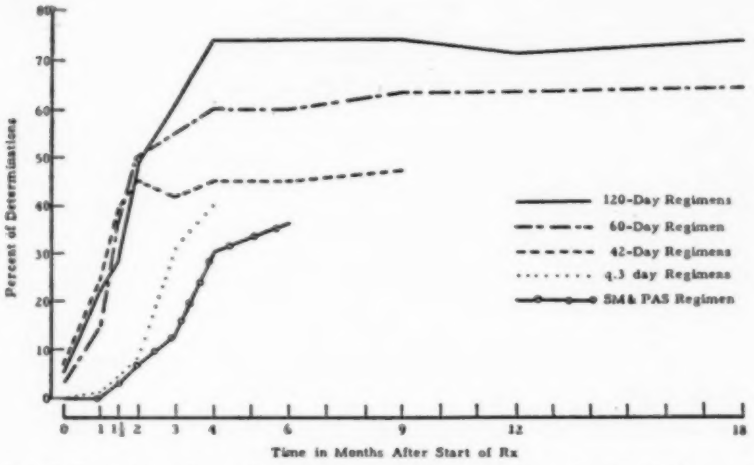


FIG. 5. Percentage of organisms resistant to 10 γ of streptomycin per ml. or more on various regimens, at different times after start of therapy.

In figure 5, data are also presented for the rate of emergence of tubercle bacilli resistant to 10 γ or more of streptomycin per ml. on a regimen of 1.0 Gm. administered every third day for 120 days. On this regimen, the rate of emergence of resistance *per day of treatment* appears to approximate closely that of daily injection, being, on the every-three-day regimen, one-third the rate of that with daily administration. Differences for this regimen from the data for the first three regimens (120, 60, and 42 days) are significant at all points in time up to 4 months after the start of therapy. Moreover, significant differences also exist at four months between these data (every-three-day regimen) and the values obtained from the 120-day and 60-day regimens.

Also shown in figure 5 are data for the rate of emergence of tubercle bacilli resistant to 10 γ of streptomycin per ml. on a combined regimen of 1.0 Gm. of

streptomycin daily and 9 to 15 Gm. daily of para-aminosalicylic acid (PAS). The percentages of organisms resistant on this regimen are significantly lower than in the case of regimens of daily streptomycin administration without PAS for all points in time except six months after the start of treatment, and at this point are significantly lower than for the 120- and 60-day regimens.

Thus, two methods appear to have promise in delaying the rate of emergence of resistant tubercle bacilli: spacing the administration of streptomycin farther apart; and combining streptomycin with such an agent as PAS, which has tuberculostatic properties of its own.

Although data were presented by individual investigators at the Seventh Streptomycin Conference, which indicate that rates of emergence of resistant strains of tubercle bacilli vary with the type of lesion which predominates in the

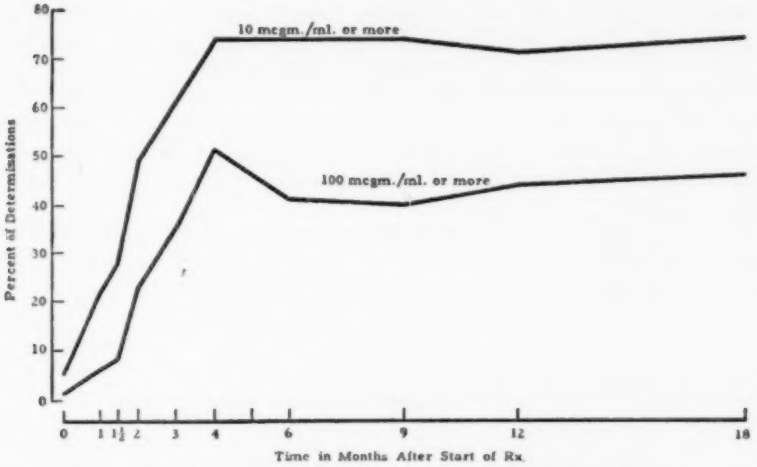


FIG. 6. Percentage of organisms resistant to 10 γ of streptomycin per ml. or more and to 100 γ of streptomycin per ml. or more on 120-day regimens only.

patient under treatment, it is not possible from the data reported to make this type of cross-tabulation until individual case reports are analyzed. It is probable, however, that the samples of cases reported for the different regimens do not differ appreciably with respect to such associated variables.

CLINICAL MATERIAL

Until analysis of cases reported on individual case report forms is complete, it is not possible to define with exactitude the composition of the clinical material treated with streptomycin as regards race, sex, and age. For the Seventh Streptomycin Conference (7) data are available for the nearly 1,500 cases of pulmonary tuberculosis most recently treated, which may be representative of the larger series. Seventy-four per cent were white; 23 per cent, Negro; and 3 per cent,

"other" or unknown. Eighty per cent were reported as aged 50 or under and 20 per cent were over 50 years of age. A very small number, probably less than 2 per cent, are female.

The remainder of this report will be concerned chiefly with an examination of results obtained in the streptomycin therapy of pulmonary tuberculosis. It is based on data from approximately 2,000 cases which were observed for at least 120 days after the start of therapy, and were treated on seven different regimens. For this purpose the two 1.0 Gm. a day for 120-day regimens (employing 5 and 2 injections a day, respectively) have been combined, as results between the two subgroups appear to be identical.

Characteristics of Cases of Pulmonary Tuberculosis

It is desirable to determine as accurately as possible whether the cases treated on the different regimens are comparable. Greater assurance of comparability would have been available had more complete random selection been carried out. Examination will be made of the following characteristics of cases of pulmonary tuberculosis at the start of treatment, on which data have been recorded: stage of the disease, course of the disease during a pre-streptomycin observation period of two or three months; cavities demonstrable; and the predominance of exudation, as judged by the individual investigators. The results are presented in figures 7 and 8.

As shown in figure 7, the percentage of cases with far advanced disease at the start of treatment varied among the seven streptomycin regimens from 67.1 to 78.4. The percentage of cases with moderately advanced disease varied from 19.7 to 28.2, and of those with minimal disease from 0 to 5.4 per cent. Whereas there is not more than a 10 per cent difference between the stages of the disease among the cases treated on these regimens, certain differences are statistically significant. The lesions of the cases treated on the first three regimens employed: 2/120[6], 2/60, and 1/120 were significantly less far advanced (68 per cent average) than those treated on the four streptomycin regimens more recently studied, *i.e.*, 0.5/120, 1/42, 0.5/42, and 1 q.3 d./120 (77 per cent far advanced). Cases treated on the 1/42 regimen were reported as far advanced significantly more frequently than those on the 0.5/42 regimen.

With respect to the percentages of cases with disease progressive prior to streptomycin therapy (figure 7), there is seen to be considerable uniformity (79 per cent) among the cases treated on four regimens: 1/120, 2/60, 0.5/120, and 1/42. The lesions in the cases treated on the 0.5/42 regimen were less progressive (73 per cent), however, and on the 2/120 and 1 q. 3d/120 regimens were least progressive (67 per cent). The latter differences are statistically significant.

In figure 8 are illustrated the values for the percentages of patients with cavernous disease and those whose disease was judged to be predominantly (more than 50 per cent) exudative. With respect to the latter characteristic, the range of

[6] Numerator of fraction indicates daily dose of streptomycin in grams; denominator indicates duration of therapy in days. The abbreviation q.3d. is used to designate "every three days."

variation of percentage of cases on different regimens is 14 per cent (from 59 to 73 per cent), with the exception of the cases treated on the 1 q. 3d./120 regimen. The lesions in the latter group were far less predominantly exudative (24 per cent) than those treated on the other regimens. Significant differences also were found between: cases treated on the 2/120 and 1/120 regimens; between those

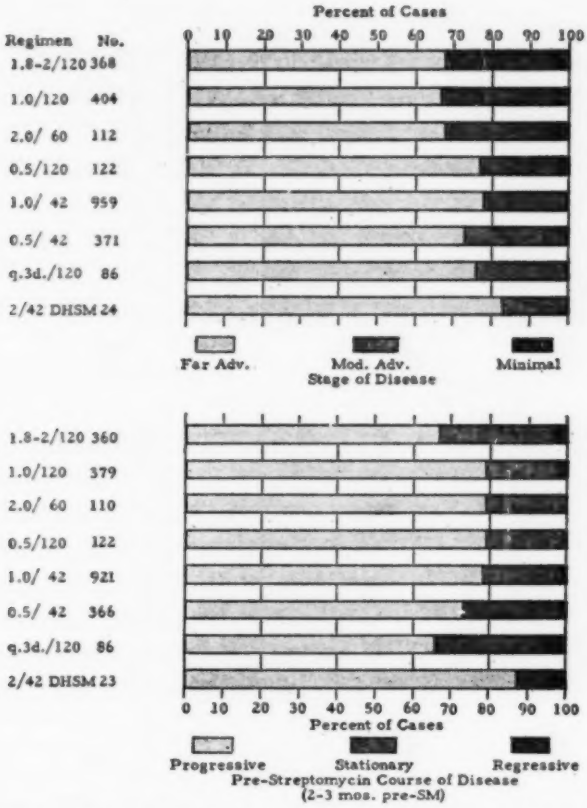


FIG. 7. Characteristics of cases of pulmonary tuberculosis treated with streptomycin (at beginning of treatment).

treated on the 0.5/120 and 0.5/42 regimens; and between those treated on the 0.5/42 and 1/42 regimens.

A peculiar situation exists with respect to the percentage of cases reported as being demonstrably cavernous (figure 8). In gathering the data for the Seventh Conference on cases treated by the last four regimens, the investigators were asked to report whether cavities were small, medium, or large in size. For pre-

vious Conferences, on cases treated by the first four regimens, information only with respect to the presence or absence of cavities was requested and recorded. As figure 8 indicates, with the two different methods of reporting, the cases treated on the last four regimens are reported to have a significantly higher percentage of cavities. If, however, the data from the Seventh Streptomycin Con-

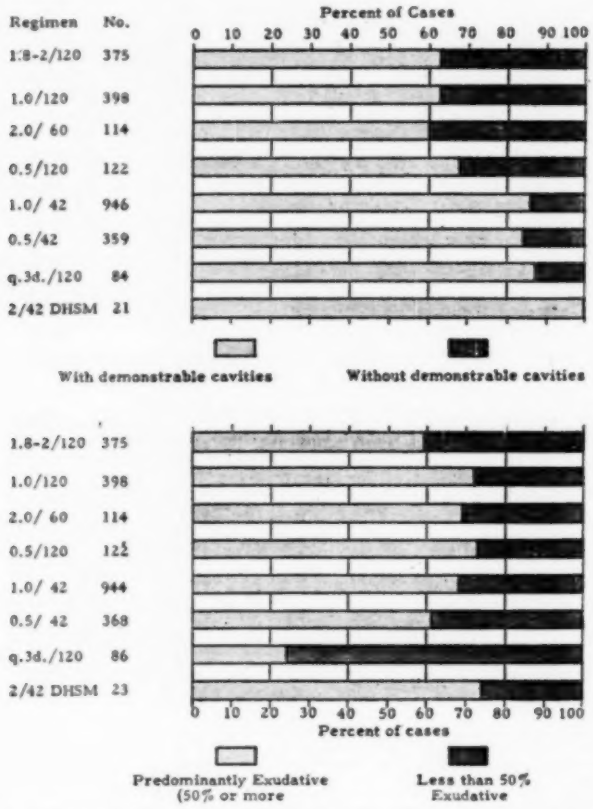


FIG. 8. Characteristics of cases of pulmonary tuberculosis treated with streptomycin (at beginning of treatment).

ference are re-examined and the cases treated on these four regimens which are reported as having small cavities are excluded, the percentages of cases reported as having *medium or large cavities* are not significantly different from those which were reported as cavernous on the first four regimens. The figures for per cent cavernous with this modification are given in table 3.

In summarizing the comparisons among the cases treated on the various regi-

mens with respect to stage, pre-streptomycin course, per cent cavernous, and per cent predominantly exudative, it is seen that a considerable degree of uniformity exists. Where differences have been indicated as being statistically significant, they have not been large in terms of percentages and the probability of the differences being significant has not been much less than 0.05.

Only one major difference has been noted: the cases treated on the 1 q. 3d./120 regimen are much less predominantly exudative than those treated on the other regimens. In addition, the disease of the 2/120 cases was slightly less far advanced and less predominantly exudative than the lesions in those treated on the other regimens, and the disease in the 0.5/42 cases was slightly less far advanced, less progressive (pre-streptomycin) and less predominantly exudative than the 1/42 cases. Although included in figures 7 and 8, data on the characteristics of the 24

TABLE 3

Characteristics of Cases of Pulmonary Tuberculosis: Cases Reported as Cavernous, with Modifications†

STREPTOMYCIN REGIMEN	NUMBER CASES REPORTED	TOTAL CAVITIES DEMONSTRABLE		NUMBER CASES REPORTED	LARGE AND MEDIUM CAVITIES DEMONSTRABLE†	
		Number	Per cent		Number	Per cent
2 Gm./day—120 days[5]*	375	235	62.6			
1 Gm./day—120 days[5]	387	253	63.0			
2 Gm./day—60 days[5]	114	68	59.9			
0.5 Gm./day—120 days[6]	122	83	68.0			
1 Gm./day—42 days[7]	(946	815	86.2)	946	626	66.2
0.5 Gm./day—42 days[7]	(359	300	83.6)	359	228	63.5
1-2 Gm. q. 3d.—120 days[7]	(84	73	86.9)	84	64	76.2
2 Gm./day—42 days *DHSM*[7]	(21	21	100.0)	21	16	76.2

* Superscript numerals indicate Streptomycin Conference from *Minutes* of which data are obtained.

† See text for explanation. These data available only for regimens reported to the Seventh Streptomycin Conference.

cases treated with dihydrostreptomycin have not been discussed in detail. In thus stressing the similarity of the cases treated on the different regimens, the assumption has been made, according to the preceding paragraph, that cases on all regimens are comparable with respect to the incidence of cavernous disease.

It is advisable, in attempting to assess the therapeutic effect of streptomycin therapy of different regimens on the groups of cases so differentiated, to keep these differences in mind. But, until correlations or cross-tabulations are available from individual case report analyses, it will be difficult to determine the extent of allowance which should be made on their account.

From data gathered for the Seventh Streptomycin Conference (7), however, in the case of the 42-day regimens, it is possible to draw certain tentative conclusions. The lesions of the more predominantly exudative cases improve more than those lesions which were judged to be less than 50 per cent exudative. Moderately

advanced lesions improve more frequently than do far advanced lesions, and the improvement is more maintained (from the 42-day point to the 120-day point). Lesions which are stationary during the pre-streptomycin observation period improve least at 42 days, but slightly more than those which are progressive before streptomycin at 120 days. Those lesions, relatively few in number, which were regressive prior to streptomycin therapy improved most frequently at both the 42-day and the 120-day point.

Results of Treatment of Pulmonary Tuberculosis

Examination will be made of the differences reported between cases of pulmonary tuberculosis treated on seven different streptomycin regimens in the following five respects: (*1*) change in certain clinical signs; (*2*) change in pulmonary lesions as determined by roentgenographic observation 120 days after the beginning of therapy; (*3*) incidence of relapse in pulmonary lesions, interpreted as worsening by roentgenographic observation after an initial improvement; (*4*) rates of "sputum conversion" by culture; and (*5*) mortality.

Change in clinical signs: Data have been collected on cases treated on eight regimens with respect to reduction of fever present at the start of therapy and weight change. Moreover, for the first three regimens explored, changes in sputum volume were recorded. The collected figures for these data are presented in table 4.

Approximately 40 per cent of patients treated on all regimens were reported as being not febrile at the time therapy was begun. In the remaining 60 per cent, febrile at the start of therapy, fever was reported as being not reduced in about one-eighth; as being reduced, but not to normal, in about one-third; and as being reduced to normal in slightly over one-half.

With respect to weight changes during the 120-day therapeutic period, the reported experience has been that 709 (38 per cent) of the 1,867 patients have had a weight gain of over 10 pounds; 68 (4 per cent) have had a weight loss greater than 10 pounds; and 1,090 patients (58 per cent) have had a weight change of between 10 pounds gain and 10 pounds loss, at the 120-day point.

Among the patients on the three regimens for which decrease in sputum volume is reported (and the amount of decrease is not known), the incidence of decrease is considerably less for those on the 60-day regimen than for those on the 120-day regimens.

Change in roentgenographic observation at 120 days: In figure 9 are shown the results of the investigators' ratings of roentgenographic change for the results of treatment on seven streptomycin regimens. In this figure are represented the percentage of cases in which the disease improved and those reported as exhibiting marked improvement.

Almost identical percentages of improvement of all degrees occurred with the first four regimens (2/120[7], 2/60, 1/120, and 0.5/120), averaging approximately 80 per cent. Improvement was noted in 75 per cent of the cases on the regimen

[7] Numerator of fraction indicates daily dose of streptomycin in grams; denominator indicates duration of therapy in days.

TABLE 4

Clinical Changes in Cases of Pulmonary Tuberculosis Treated with Streptomycin on Various Regimens during 120-day Treatment Period

CLINICAL OBSERVATION	STREPTOMYCIN REGIMENS											
	2 Gm./day 120 days 5*			1 Gm./day 120 days 5*			2 Gm./day 60 days 5*			0.5 Gm./day 120 days 6*		
	Febrile Beg. Rx		All Cases	Febrile Beg. Rx		All Cases	Febrile Beg. Rx		All Cases	Febrile Beg. Rx		All Cases
	No.	%	%	No.	%	%	No.	%	%	No.	%	%
Temperature during Therapy												
Reduced to normal	135	58		166	64		16	40		37	51	
Reduced but not to normal	61	26		67	25		14	35		20	28	
Not reduced	37	16		28	11		10	25		15	21	
Tot. Temp. Elev. Beg. Rx	233	100	62	261	100	66	40	100	51	72	100	59
Temp. not Elev. Beg. Rx	142		38	137		34	39		49	50		41
All Cases Treated	375		100	398		100	79		100	122		100
	No.	%		No.	%		No.	%		No.	%	
Wt. During 120-d. Period												
Wt. gain over 10 lbs.	155	41		179	45		17	21		50	41	
Wt. change between gain 10 lbs. and loss 10 lbs.	204	54		198	50		55	70		67	55	
Wt. loss over 10 lbs.	16	5		21	5		7	9		5	4	
All Cases Treated	375	100		398	100		79	100		122	100	
Change in Sputum Volume												
Decreased in volume	266	71		295	74		34	43		†	†	
Not decreased in volume	109	29		103	26		45	57		†	†	
All Cases Treated	375	100		398	100		79	100		122	100	

CLINICAL OBSERVATION	STREPTOMYCIN REGIMENS											
	1 Gm./day 42 days 7*			0.5 Gm./day 42 days 7*			1–2 Gm. q. 3d. 120 days 7*			2 Gm. *DHSM*‡/d. 42 days 7*		
	Febrile Beg. Rx		All Cases	Febrile Beg. Rx		All Cases	Febrile Beg. Rx		All Cases	Febrile Beg. Rx		All Cases
	No.	%	%	No.	%	%	No.	%	%	No.	%	%
Temperature During Therapy												
Reduced to normal	346	54		101	46		29	74		5	33	
Reduced but not to normal	235	36		85	38		7	18		10	67	
Not reduced	66	10		36	16		3	8		0	0	
Tot. Temp. Elev. Beg. Rx	647	100	67	222	100	59	39	100	45	15	100	63
Normal or Unknown Beg. Rx	315		33	152		41	47		55	9		37
All Cases Treated	962		100	374		100	86		100	24		100

TABLE 4—*Concluded*

CLINICAL OBSERVATION	STREPTOMYCIN REGIMENS							
	1 Gm./day 42 days 7*		0.5 Gm./day 42 days 7*		1–2 Gm. q. 3d. 120 days 7*		2 Gm. *DHSM*‡/d. 42 days 7*	
	No.	%	No.	%	No.	%	No.	%
Wt. During 120-d. Period								
Wt. gain over 10 lbs.	202	35	80	33	26	33	0	0
Wt. change between gain 10 lbs. and loss 10 lbs.	358	63	155	65	51	65	2	100
Wt. loss over 10 lbs.	12	2	6	2	1	2	0	0
All Cases Treated	572	100	241	100	78	100	2	100

* Numerals designate number of Streptomycin Conference from *Minutes* of which data are obtained.

† Data on changes in sputum volume available only for first three regimens, reported in *Minutes* of Fifth Streptomycin Conference.

‡ DHSM = Dihydrostreptomycin.

employing 1.0 Gm. a day every 3 days for 120 days; in 70 per cent of those on 1.0 Gm. a day every day for 42 days; and in 60 per cent of the cases treated with 0.5 Gm. a day for 42 days. Only the results on the last named three regimens are statistically significantly different, both from the first four regimens mentioned and among each other, with respect to all improvement of pulmonary lesions by roentgenographic observation between the start of treatment and 120 days thereafter. Table 5 presents the data of figure 9 as to the percentages of all improvement by roentgenographic observation, arranged according to the two variables in the regimens. The daily dose of streptomycin is presented in the horizontal axis, and the duration of therapy in the vertical.

If the reports of change on roentgenographic observation indicated as moderate improvement and marked improvement (including very marked improvement) are analyzed in a similar manner, however, a number of differences between regimens are found to be significant (table 6). Moderate and marked improvement is more frequent on the 2/120 regimen (66 per cent) than on the 2/60 regimen (52 per cent); on the 1/120 regimen (64 per cent) than on the 1/42 regimen (47 per cent); on the 0.5/120 regimen (57 per cent) than on the 0.5/42 regimen (41 per cent); on the 1/120 regimen (64 per cent) than on the 0.5/120 regimen (57 per cent); on the 2/60 regimen (52 per cent) than on the 1/42 regimen (47 per cent); and on the last named regimen than on the 0.5/42 regimen (41 per cent). Significant differences were lacking only between the following regimens: 2/120 and 1/120, and 0.5/120 and 1 q. 3 d./120.

Referring to the preceding section on the relative roentgenographic improvement which could be anticipated from the differences in the characteristics of the disease, it will be observed that the 2/120 cases had the highest incidence of marked and moderate improvement (66 per cent), in spite of characteristics leading to the anticipation of relatively less improvement. Moreover, the cases

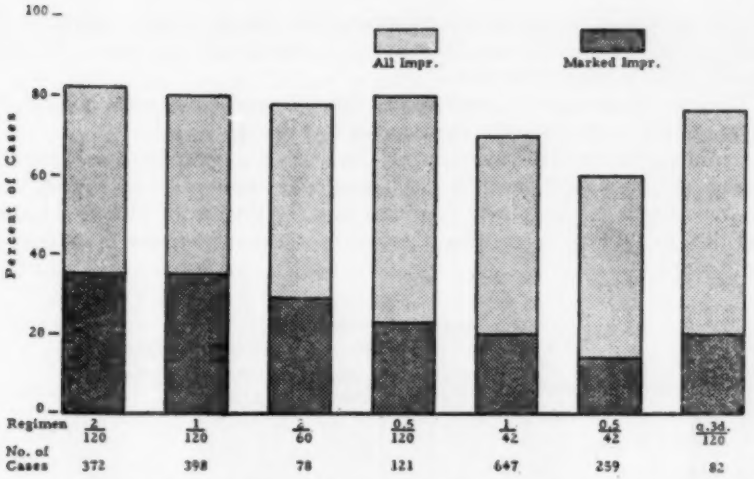


FIG. 9. Percentage of improvement by roentgenographic observation in cases of pulmonary tuberculosis treated with streptomycin on various regimens (all observations 120 days after start of therapy).

TABLE 5

Comparison of Roentgenographic Improvement at 120 Days among Seven Streptomycin Regimens in the Treatment of Pulmonary Tuberculosis

DURATION OF TREATMENT, DAYS	DAILY DOSE STREPTOMYCIN, GM.			
	2	1	½	q. 3d.
	(*Per cent of Cases*)			
120	82	– 80	– 80	– 76
	|	*	*	
60/42	79	– 70	* 60	—

* Difference between adjacent pairs statistically significant.
– Difference between pairs not statistically significant.

TABLE 6

Comparison of Marked and Moderate Improvement by Roentgenographic Observation at 120 Days among Seven Streptomycin Regimens in the Treatment of Pulmonary Tuberculosis

DURATION OF TREATMENT, DAYS	DAILY DOSE STREPTOMYCIN, GM.			
	2	1	½	q. 3d.
	(*Per cent of Cases*)			
120	66	– 64	* 57	– 49
	*	*	*	
60/42	52	* 47	* 41	—

* Difference between adjacent pairs statistically significant.
– Difference between pairs not statistically significant.

treated on the 1/42 and 0.5/42 regimens, with characteristics leading to the anticipation of relatively more improvement, actually had the lowest. This was most marked in the 0.5/42 cases.

These results are again illustrated, in a three-dimensional manner, in figure 10. From these data the following patterns begin to emerge:

a. Among the four 120-day regimens, there is only a slight decrease in the percentage of "all" improvement by roentgenographic observation as the daily dose of streptomycin is successively decreased from 2.0 Gm. to 1.0 Gm. to 0.5 Gm., and then to 1.0 Gm. every three days; no one of the differences is statistically significant.

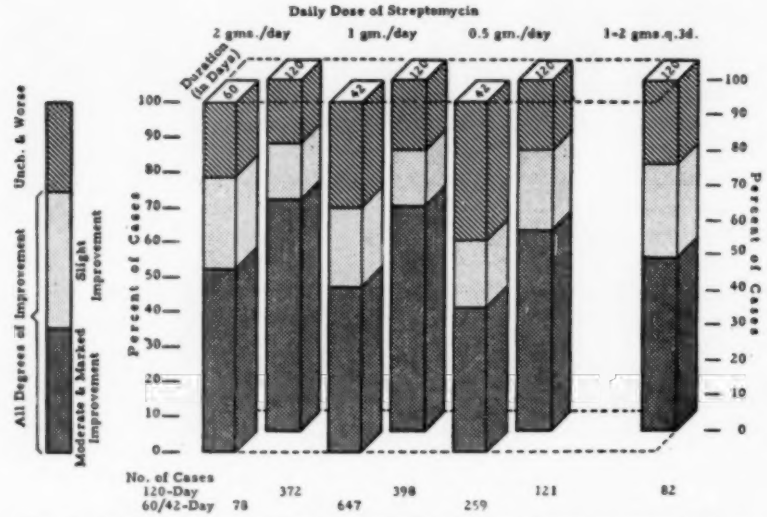


FIG. 10. Comparison of improvement in differing degrees by roentgenographic observation among seven streptomycin regimens in the treatment of pulmonary tuberculosis, according to daily dose and duration of therapy.

b. Among the same four regimens, there is more decrease with respect to the incidence of "marked and moderate" improvement with decrease in daily dosage, although the differences are statistically significant only between the 1/120 and 0.5/120 cases.

c. Among the three regimens of less than 120 days' duration, there is significantly less improvement (of "marked and moderate" degree) on the two 42-day regimens than on the 2/60 regimen; and, on regimens of 42-day duration there is significantly less improvement of "any" degree or of "marked and moderate" degree when the daily dose is decreased from 1.0 to 0.5 Gm. a day. With these regimens of shorter duration, the effect of decreasing daily dosage of streptomycin appears to be more marked than in the case of regimens of 120 days' duration.

d. When regimens of identical daily dosage are compared, there is in every instance a significant decrease in the per cent of cases reported as "markedly and moderately" improved as duration is decreased from 120 days to 60 or 42 days; and, in addition, a significant decrease for both the 1.0 Gm. per day and the 0.5 Gm. per day comparisons for "all" degrees of roentgenographic improvement as duration is shortened from 120 to 42 days.

1948 jury review: A brief word may be added concerning the roentgenographic changes found by a "jury" which in March 1948 (5) conducted a review of pulmonary tuberculosis cases treated on three streptomycin regimens.

There was no statistical difference between improvement in any degree or any combination of degrees at the 120-day point among cases treated on the three regimens reviewed: 2.0 Gm. per day for 120 days, 2.0 Gm. per day for 60 days, and 1.0 Gm. per day for 120 days.

The mechanics of the jury review made it possible to make comparisons both at 60 days and at 120 days after the start of streptomycin therapy. Comparison of results at the 60-day point between the two 2.0 Gm. per day regimens, both therefore treated identically up to this point, indicated that in all probability the cases selected for treatment on the 2.0 Gm. per day for 120-day regimen differed significantly from those selected for treatment on the 2.0 Gm. per day for 60-day regimen. For there was significantly less improvement in the former cases.

The jury review indicated that at 60 days treatment with 2.0 Gm. per day is superior to that with 1.0 Gm. per day, for the differences at this point in time between these two regimens are statistically significant for all degrees of improvement. As the report of this jury review points out, however (5), the least amount of improvement occurs with the 2.0 Gm. per day for 60-day regimen between the 60-day point and the 120-day point, so that the percentages of improvement at 120 days between the two regimens are not significantly different. If further observation and analysis substantiate this conclusion, it might be concluded that larger doses for shorter periods of time lead to results equal to those of smaller doses for longer periods of time, in the range of the variables covered by the jury review.

Relapse rates by roentgenographic observation: Figure 11 gives the rates for relapse by roentgenographic observation, defined as worsening after initial improvement, for cases treated on the seven streptomycin regimens. A considerable uniformity of rate of relapse as a function of time is reflected by these figures, especially for the 2/120[8], the 2/60, the 1/120, and the 1 q. 3d./120 regimens. Differences between these rates are not statistically significant. In figure 11 only one curve is used to depict the relapse rates for both 42-day regimens as they are practically identical. The relapse rates for these two regimens, and for the 0.5 Gm. per day for 120-day regimen, are in all probability significantly higher than for the other regimens, although the possibility of differences in reporting must always be taken into account. When results from individual case report forms are available, and it is possible to be more certain of the accuracy of these observations

[8] Numerator of fraction indicates daily dose of streptomycin in grams; denominator indicates duration of therapy in days.

than in such summary reporting as has been in use, it is quite possible that a just basis will be provided for the reserve with which investigators have employed the regimens of these lower total dosages.

"Sputum conversion": Figure 12 gives the data for "sputum conversion" by culture. The criterion for conversion was "negative sputum" and/or gastric cultures for a minimum period of three months. There is again a considerable uniformity in this regard among the cases treated on the different regimens. Until individual case analysis data are available, it has not been felt worth while to subject these data to statistical analysis.

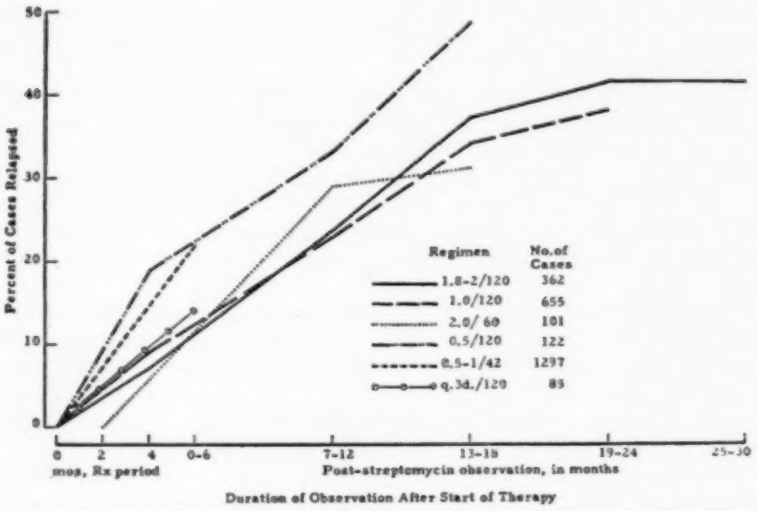


FIG. 11. Rates of relapse (worsening after improvement) by roentgenographic observation in streptomycin-treated cases of pulmonary tuberculosis (according to regimen and duration of observation).

Table 7 may be studied in conjunction with figure 12, for it gives the frequencies with which collapse therapy is reported as having been used on the different regimens at different points in time. Data on the various types of collapse employed are not available. In general, less collapse therapy was employed in the earlier regimens, and the apparently higher "sputum conversion" rates noted for the two 42-day regimens (top curve in figure 12) may well be more related to the higher frequency with which collapse was employed in these cases than to the streptomycin therapy. Much more thorough analysis will be required to clarify the relative effects of collapse therapy and of streptomycin therapy on "sputum conversion" rates.

Mortality: Figure 13 gives the data for cumulative mortality rates. It is to be noted that the three lowest rates are those for the three regimens with the largest total dosages (2.0 Gm. per day for 120 days, 1.0 Gm. per day for 120 days,

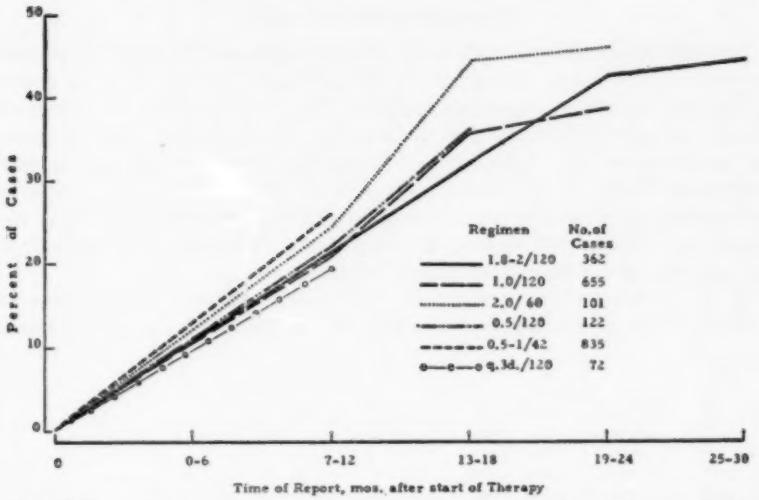


FIG. 12. Rate of sputum conversion by culture in streptomycin-treated cases of pulmonary tuberculosis at various intervals after start of treatment (according to regimen).

TABLE 7

Employment of Collapse Therapy in Patients with Pulmonary Tuberculosis Treated with Streptomycin on Various Regimens

STREPTOMYCIN REGIMEN	DURING TREATMENT PERIOD (120 days)			TIME OF REPORT AFTER THE END OF TREATMENT											
				7–12 months			13–18 months			19–24 months			25–30 months		
	No. Patients Followed	Collpsd.		No. Patients Followed	Collpsd.		No. Patients Followed	Collpsd.		No. Patients Followed	Collpsd.		No. Patients Followed	Collpsd.	
		No.	%		No.	%		No.	%		No.	%		No.	%
2 Gm./day—120 d.	375[5]*	12	3.2												
1 Gm./day—120 d.	398[5]	45	11.3	398[5]	132	33.1	375[5]	113	30.1	362[5]	157‡	43.5	226[7]	155‡	47.4
2 Gm./day—60 d.	114[5]†	1	0.9	114[5]	39	34.2	655[5]	299‡	45.7	670[7]	358‡	53.5			
0.5 Gm./day—120 d.	122[5]	6	4.9	122[5]	46	37.7	101[5]	48‡	47.4	122[7]	60‡	49.3			
1 Gm./day—42 d.	691[7]	423	61.2				134[7]	66‡	49.7						
0.5 Gm./day—42 d.	281[7]	144	51.2												
1–2 Gm. q. 3 d. for 120 days	53[7]	24	28.9												
Totals to date	2,064	655	31.3	634	217	34.2	1,265	526	41.6	1,154	575	49.9	326	155	47.4

* Superscript numerals identify Streptomycin Conferences from *Minutes* of which data are obtained.

† Data "during treatment period" for this regimen only for 60 days (not 120 days).

‡ Number of collapse cases calculated as follows: per cent collapsed during treatment (first column) added to per cent collapsed since end of treatment (from *Minutes* of Streptomycin Conferences), to give total per cent collapsed; this per cent applied to number of cases followed to give number of cases collapsed.

and 2.0 Gm. per day for 60 days). In figure 13 the mortality rates for the two 42-day regimens and that for the 0.5 Gm. per day for 120-day cases are significantly higher than for the cases studied on the three earlier regimens.

Extrapulmonary Tuberculosis

It would be desirable to analyze the effects of different streptomycin regimens on various tuberculous conditions in a manner similar to that in which cases of pulmonary tuberculosis have been analyzed. This is not possible in most instances for the two principal reasons that the number of cases of each condition treated on each regimen have been relatively small and the data defining the extrapulmonary conditions are less complete. It is therefore necessary to make certain assumptions, such as that cases treated on different regimens are roughly comparable in all important respects, and to interpret differences noted with greater reserve than in the case of pulmonary tuberculosis.

In a few tuberculous conditions treated with streptomycin, such as tuberculosis of the alimentary tract, tuberculosis of the pericardium, peritoneum,

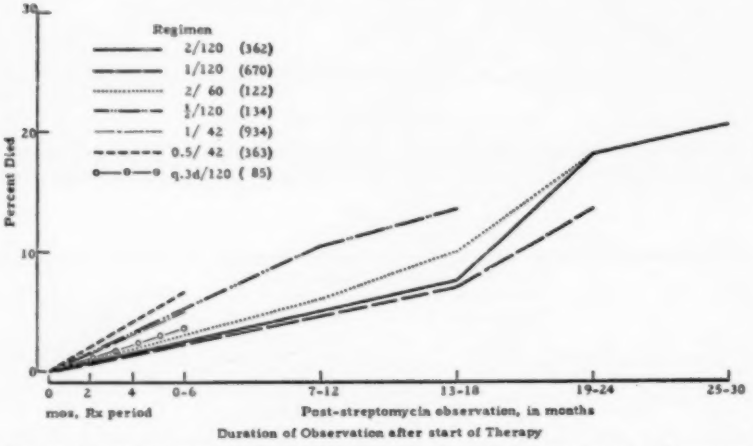


FIG. 13. Mortality rates in streptomycin-treated cases of pulmonary tuberculosis, according to regimen and duration of observation.

skin, eye, and ear, results have been reported to successive Streptomycin Conferences in summary form disregarding differences in results according to streptomycin regimen. In these conditions individualized types of analyses have been required. Streptomycin-treated cases of tuberculous enteritis (8) and of tuberculous peritonitis (9) have been so studied and reported, and studies are now under way in the instance of tuberculous pericarditis (10), tuberculous otitis media (11), tuberculosis of the skin (12), and of the eye (13).

Tuberculous tracheobronchitis, laryngitis, lymphadenitis, and sinuses and fistulae: Table 8 presents figures for the incidence of healing, improvement, absence of change, and worsening, in cases of tuberculous tracheobronchitis, laryngitis, sinuses and fistulae, and lymphadenitis, according to the streptomycin regimens employed.

TABLE 8

Changes in other Tuberculous Lesions Treated on Various Streptomycin Regimens During Treatment Period (120 Days)

TUBERCULOUS CONDITION	STREPTOMYCIN REGIMENS															
	2 Gm./day 120 days (5*)		1 Gm./day 120 days (5*)		1 Gm./day 42 days (7*)		0.5 Gm./day 42 days (7*)		0.5 Gm./day 120 days (6*)		0.2 Gm./day 120 days (6*)		0.2 Gm./day 42 days (7*)		All Cases (5–7*)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Tracheobronchitis																
Healed	31	46	32	71	40	67	20	51							123	59
Improved	28	42	8	18	11	18	17	44							64	30
Healed and Improved	59	88	40	89	51	85	37	95							187	89
Unchanged	7	10	3	7	1	2	2	5							13	6
Worse	1	2	1	2	0	0	0	0							2	1
Unknown	0	0	1	2	8	13	0	0							9	4
Total Cases	67	100	45	100	60	100	39	100							211	100
Laryngitis																
Healed	23	38	49	56	34	39	22	54	6	28					134	45
Improved	28	46	32	38	21	24	14	34	13	62					108	36
Healed and Improved	51	84	81	92	55	63	36	88	19	90					242	81
Unchanged	5	8	2	2	22	25	3	7	0	0					32	11
Worse	0	0	1	1	8	9	2	5	1	5					11	4
Unknown	5	8	4	5	2	3	0	0	1	5					11	4
Total Cases	61	100	88	100	87	100	41	100	21	100					296	100
					(Fistulae only)		(Sinuses, ā retreatment)						(Sinuses, ā retreatment)			
Sinuses and fistulae																
Healed	110	87	163	70	14	74	17	76	9	60	2	67	6	55	320	75
Improved	10	8	56	23	3	16	3	14	6	40	1	33	3	27	82	19
Healed and Improved	120	95	218	93	17	90	20	90	15	100	3	100	9	82	402	94
Unchanged	5	4	16	7	1	5	1	5	0	0	0	0	0	0	23	5
Worse	1	1	0	0	1	5	1	5	0	0	0	0	2	18	5	1
Total Cases	126	100	234	100	19	100	22	100	15	100	3	100	11	100	430	100
	2 and 1 Gm./day 120 days				(acute only)		(acute only)									
	No.	%														
Lymphadenitis																
Disappeared	12	33			0	0	3	33							15	21
Improved	18	50			14	56	4	45							36	52
Disappeared and Improved	30	83			14	56	7	78							51	73
Unchanged	4	11			11	44	2	22							17	24
Worse	2	6			0	0	0	0							2	3
Total Cases	36	100			25	100	9	100							70	100

* Numerals designate number of Streptomycin Conference from *Minutes* of which data are obtained.

Examination of the figures in tuberculous tracheobronchial and laryngeal lesions during the 120-day treatment period reveals some inconsistencies, indicating that cases treated on different regimens may not have been entirely comparable, but they do reflect a generally favorable response of these conditions to streptomycin therapy in all variations of regimen investigated. Results in the treatment of tuberculous laryngitis appear slightly less satisfactory than in the treatment of tuberculous tracheobronchitis. Accurate data are not available with which to compare variations in therapeutic response with the type of lesion present at the start of treatment. When healing occurred, it did so, on the average, after six to eight weeks of therapy.

According to the figures in table 8, the response of both tuberculous sinuses and fistulae (the latter defined as communicating with a body cavity) to streptomycin therapy, with respect to per cent improved and healed, is uniformly excellent. With respect to the per cent healed (excluding those which merely improved), there may be a slightly less favorable response in cases treated on the regimens of smaller daily dosage. At the Seventh Streptomycin Conference a report was made from the Veterans Administration Hospital, Oteen, North Carolina (14), on results of treatment with 0.2 Gm. a day for 42 days. This analysis appeared to indicate that, on a daily dosage of this order, draining tuberculous sinuses respond less rapidly and less favorably to streptomycin than on regimens of larger daily dosage, and that 0.2 Gm. of streptomycin a day is at or near the lower level of therapeutic efficacy for this condition.

The data in table 8 for tuberculous lymphadenitis treated with streptomycin are relatively inconclusive, although it is suggested that the results of treatment with smaller doses for shorter periods of time are slightly inferior to those of treatment with larger doses for longer periods of time.

Genitourinary tuberculosis: A special study of cases of genitourinary tuberculosis treated with streptomycin has been made at the Veterans Administration Hospital, Bronx, N. Y. (15).[9] Figures compiled for the Fifth, Sixth, and Seventh Streptomycin Conferences (5, 6, 7) suggest that there are no important differences according to streptomycin regimen (2.0 Gm. and 1.0 Gm. a day for 120 days, 1.0 Gm. and 0.5 Gm. a day for 42 days) for the following observations: disappearance and improvement of urinary symptoms; changes in pyelographic and cystoscopic observations; and changes in genital lesions. Improvement in urinary symptoms is reported in approximately 90 per cent of all treated cases, in cystoscopic observations in approximately 80 per cent, in genital lesions in approximately 50 per cent (in many instances associated with surgical procedures), and in pyelographic observations in approximately 25 per cent.

Figure 14 shows the "urinary conversion" rates by culture of 140 cases of genitourinary tuberculosis treated on three regimens, in all of which urines positive for tubercle bacilli were demonstrated at the start of treatment. According to this criterion of the results of streptomycin therapy, which is more objective

[9] In this article the authors have made a detailed analysis of these streptomycin-treated genitourinary cases. The reader is referred to it for more careful assessment of the variables of treatment of genitourinary tuberculosis than is here possible.

and probably of more clinical significance than those referred to in the preceding paragraph, it is observed that a regimen of larger daily dosage and longer duration (2.0 Gm. a day for 120 days) appears to exert a more favorable influence on the results. Probably because the numbers of cases treated on the different regimens are not large, the differences between the percentages of "urinary conversion" indicated are significant in only one instance. The percentage of cases with urine "converted" at 120 days after the start of treatment on the regimen of 2.0 Gm. a day for 120 days (83 per cent of 65 cases) is significantly greater than the percentage of cases with urine "converted" on the regimen of 1.0 Gm. a day for 42 days (55 per cent of 40 cases). Differences between the percentages

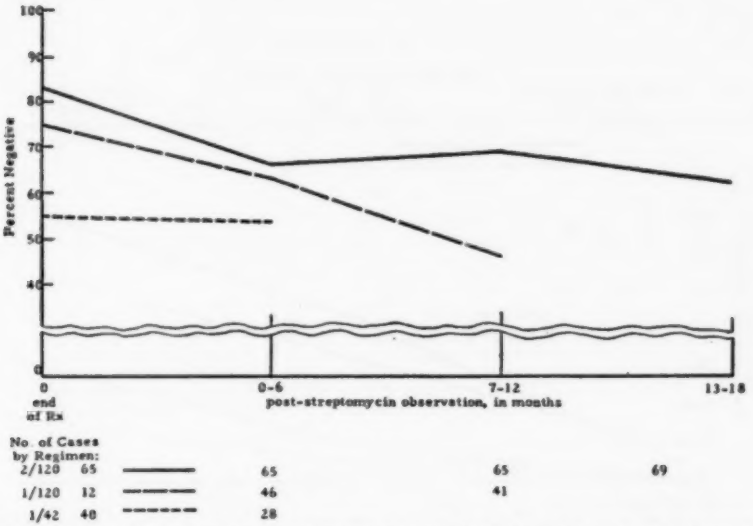


FIG. 14. Percentage of urines negative for tubercle bacilli by culture in streptomycin-treated patients with genitourinary tuberculosis during post-treatment follow-up period.

of "urinary conversion" during the follow-up period indicated in figure 14 are not significant in any instance.

Tuberculosis of bone, joint, and cartilage: In cases of tuberculosis of bone, joint, and cartilage reported to the Fifth, Sixth, and Seventh Streptomycin Conferences (5, 6, 7), the cooperating investigators were reluctant to draw conclusions as to the significance of results obtained with the several regimens. A review of approximately 100 cases, conducted in March 1948 and previously reported (3), has therefore been relied upon to a considerable extent. It indicated that, whereas 6 per cent of the lesions were improving and 70 per cent becoming worse prior to streptomycin therapy, 40 per cent of the lesions improved during the 120-day therapeutic period and 70 per cent showed improvement, as compared with the condition at the start of therapy, at the end of a post-streptomycin observation

period averaging 4 months (8 months from the start of therapy). It is planned that another review of such cases, with a longer follow-up period, will be carried out in the autumn of 1949.[10]

From the data gathered at the review of cases of tuberculosis of bone, joint, and cartilage conducted in March 1948 (16), additional analysis has indicated that results of streptomycin treatment in these conditions may be superior with 2.0 Gm. a day to those with 1.0 Gm. a day; and that longer duration of therapy (over 120 days) may be associated with a greater frequency of improvement by roentgenographic observation than shorter durations of therapy (under 120 days). Figures 15 and 16 present these data. Because the number of lesions reviewed was relatively small (105), statistical tests do not prove that the observed differ-

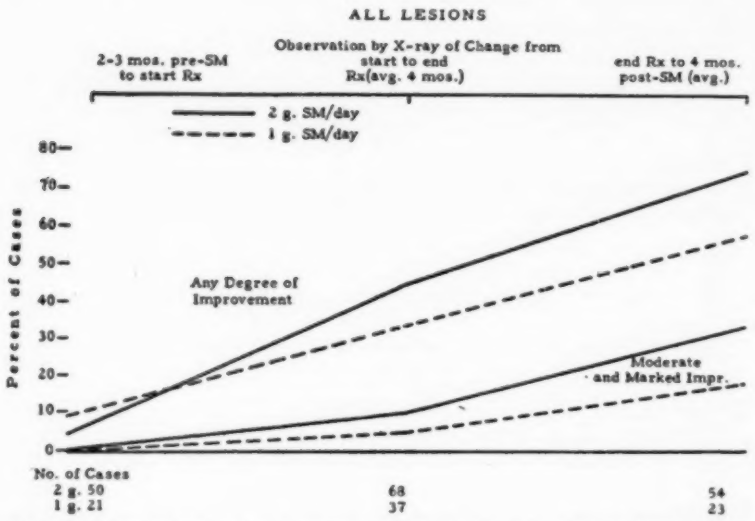


FIG. 15. Effect of dosage on incident and rate of roentgenographic improvement of tuberculosis of bones and joints treated with streptomycin (1.0 to 2.0 Gm. for 100 to 102 days in 85 per cent of cases). Review by Doctor Ghormley.

ences between the regimens are significant. If the trends noted continue in the larger series which is to be reviewed, however, the differences would acquire increasing statistical significance.

Miliary tuberculosis and tuberculous meningitis: Patients with miliary tuberculosis and tuberculous meningitis have been treated on a variety of therapeutic regimens. The majority of patients have received at least 2.0 Gm. a day of streptomycin intramuscularly, and patients with tuberculous meningitis have received, in addition, 50 mg. (originally 100 mg.) of streptomycin intrathecally three times a week.

[10] This review was held September 17–18, 1949. The results will be published in the *Minutes* of the Eighth Streptomycin Conference, November 10–13, 1949, Atlanta, Georgia.

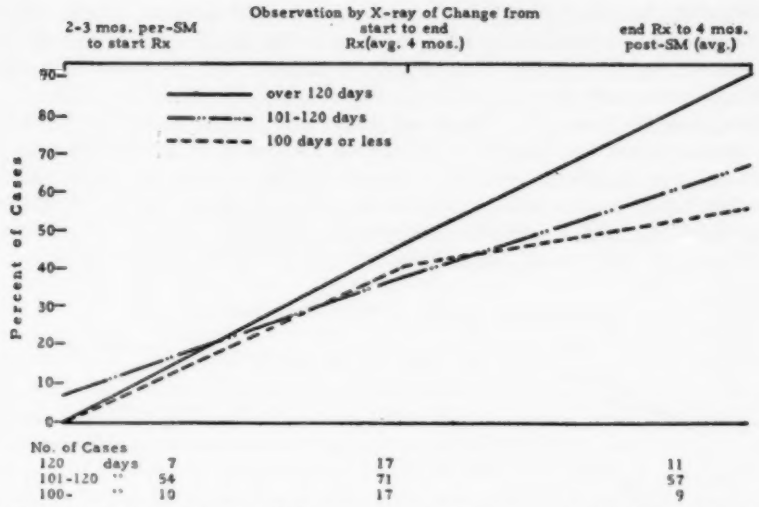


FIG. 16. Effect of duration of therapy on rate of roentgenographic improvement of tuberculosis of bones and joints treated with streptomycin, all lesions (1.0 to 2.0 Gm. for 100 to 120 days in 85 per cent of cases). Review by Doctor Ghormley.

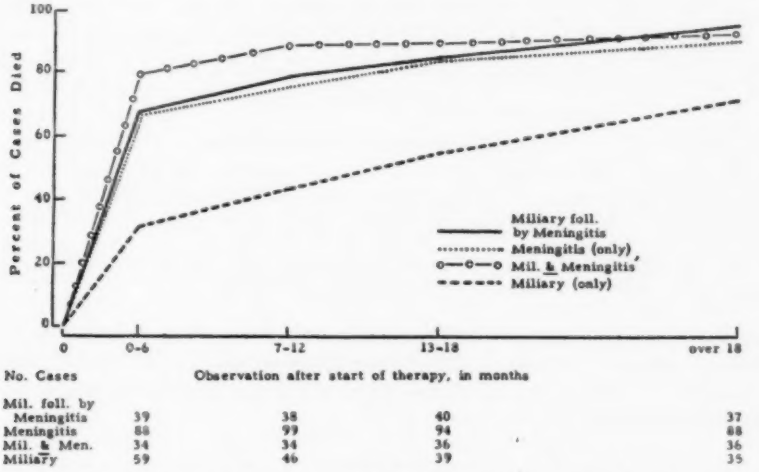


FIG. 17. Cumulative mortality of cases of miliary tuberculosis and tuberculous meningitis treated with streptomycin, at various intervals after the start of therapy.

An analysis of the first 100 cases treated has been made (17) and a follow-up of the same group was carried out in the spring of 1949 (18). Results of the 234 cases which have been treated and reported to date, presented only with respect to cumulative mortality, are given in figure 17.

With the increasing realization that comparatively favorable initial results are tempered by a steadily mounting death rate with the passage of time, usually because of the development of meningitis in patients who previously had acute miliary tuberculosis and relapses in those with meningitis, a number of variations of streptomycin therapy have been explored. These include: interrupted therapy in various forms; the omission of intrathecal therapy; and the combined use of two or more antimicrobial drugs. Data permitting cross-tabulations of results are only available with respect to the latter, and these are presented in figure 18. The chief drug used in addition to streptomycin in this series has been Promin (sodium p,p′ -diamino-diphenylsulfone-N,N′ didextrose sulfonate), given intra-

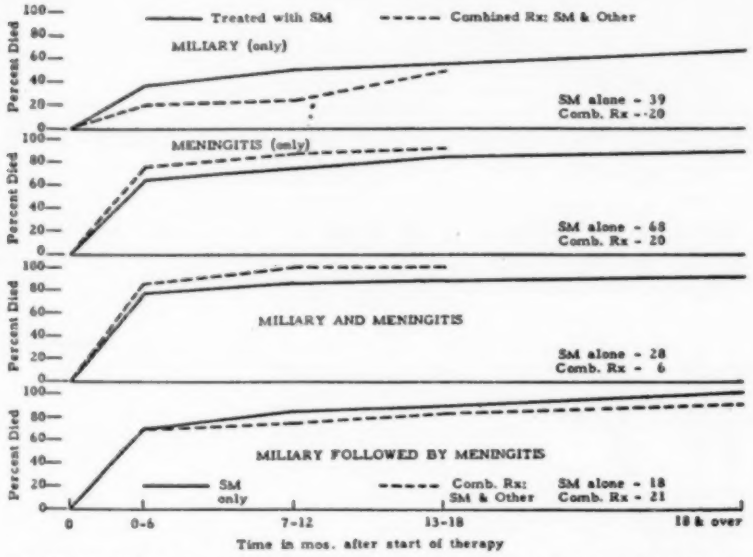


FIG. 18. Mortality of cases of miliary and meningeal tuberculosis treated with streptomycin and combined therapy, at intervals after start of therapy.

venously in a daily dosage of 4.0 Gm. during two of every three weeks. Figure 18 does not suggest that such combined chemotherapy has improved the mortality experience in miliary and meningeal tuberculosis over that for treatment with streptomycin alone.

DISCUSSION

It has been the primary purpose of the cooperative investigation to explore in a systematic manner the effects of a relatively restricted number of variables in the treatment of tuberculosis. These have been particularly the variables of streptomycin regimens, of variations in dosage, and duration of therapy. Access through the cooperating Study Units to a relatively large volume of clinical

data, selected, treated, and reported under uniform conditions, has made it possible to gather in a short time data which are more significant than usually is possible without such a coordinated study.

In addition to the larger objectives of the study, within the framework of the larger investigation, individual cooperating investigators have the opportunity, and are in fact encouraged, to explore problems subsidiary to the larger problem. Such smaller investigations may have the disadvantage of smaller size, but have the advantages of more intensive and uniform examination of results than is possible in the study as a whole, and several such studies have pointed the way for the larger investigation at opportune moments.

Evaluation of results in the treatment of tuberculosis: The problem of the evaluation of *any* form of therapy is not an easy one in so chronic and variable a disease as tuberculosis. It probably is not an unfair statement to say that no uniform or standard method of reporting results of treatment of any form of tuberculosis has been devised. There is not agreement as to which criteria are the most important or relatively most important. The usual appraisal is a composite of a number of clinical observations, such as roentgenographic change, sputum examination, clinical signs, and erythrocyte sedimentation rate. In the final analysis *survival without detectable reactivation of the disease under essentially "normal" socio-economic conditions* is the criterion for success of therapy. But obviously there are gradations of efficacy short of this end result which are recognized as satisfactory, and such a criterion, if solely relied upon, cannot be applied until many years have passed. There is serious need for accurate evaluation of all available clinical data at all stages of the treatment of the disease in order that as accurate prediction of later results may be made as possible and in order that new regimens of therapeusis may be evaluated with as much promptness and validity as possible.

The history of the cooperative streptomycin investigation of the Veterans Ad-Administration, Army, and Navy has been in large part a study of such difficulties of evaluation. Investigators have been under the opposed pressures of a natural desire to apply their results, premature as they may be, to clinical material, and of caution and patience in modifying regimens in the scientific interests of the study as a whole.

Conclusions drawn or inferred from data reported have in some instances differed from impressions and estimates of individual investigators and it has not been possible to disregard the latter entirely, for no sets of figures can completely represent clinical experience.

Results of streptomycin treatment of pulmonary tuberculosis have been presented with respect to such criteria as clinical signs, change by roentgenographic observation during the therapeutic period, relapse by roentgenographic observation during the post-streptomycin observation period, "sputum conversion" at various points in time, and the mortality experience to date. While it may be expected that there will be disagreement as to the relative clinical importance of these observations, a few relative weightings are increasingly apparent.

The initial optimism engendered by the prompt defervescence of patients with

acute forms of tuberculosis when streptomycin therapy is begun has been tempered by the realization that this initial response may generally be anticipated and still have little relationship to a reasonably satisfactory subsequent clinical course. To a lesser extent, the initially favorable roentgenographic response of pulmonary tuberculous lesions is likewise tempered by a steadily mounting percentage of relapse during and subsequent to streptomycin therapy.

Suppression of multiplication of tubercle bacilli in the body as a result of streptomycin therapy is reflected initially by "conversion" of sputum and urine, cessation of drainage from sinuses, et cetera, in a considerable percentage of cases. But it is probable that all tuberculous foci in the body are never eliminated with streptomycin therapy, and the reappearance of tubercle bacilli from the same sources likewise limits the significance of this initial response.

Such clinical responses to streptomycin must be interpreted in the light of known facts and many others need to be determined. The emergence of streptomycin-resistant strains of tubercle bacilli undoubtedly is one of the most important limiting factors in such chemotherapy. The demonstrated inability of streptomycin to have an appreciably favorable influence upon lesions with a large necrotic component is another. Undoubtedly tuberculous lesions of different tissues and organs respond to streptomycin therapy in dissimilar fashion for reasons not completely understood. Investigation is needed as to the role which other factors may play, such as those of age, race, degree of disability of the host, concomitance of multiple tuberculous lesions, and probably others as yet unsuspected.

In pulmonary tuberculosis there are indications that the less acute forms, those which might be termed subacute, respond approximately as well to streptomycin as do the acute, and that even in the chronic forms, for these are almost never devoid of some acute component, some improvement may occur. In the more chronic stages of the disease, however, relapse is more likely to occur than in the more acute stages and, when streptomycin is employed in chronic disease, it is of the utmost importance to combine it with other suitable procedures such as collapse and excisional therapy in a well-integrated therapeutic program. Additional investigations are needed to determine the optimal manner in which such combined therapy may be applied.

With so many unanswered problems remaining in the streptomycin treatment of tuberculosis, results of investigation such as those which have been presented must be regarded as preliminary, and restricted in their significance. Yet the study, through the conditions of its formation, has, it is believed, made possible certain conclusions of value, with respect to the relatively few variables on which it has concentrated.

Statistical considerations: Hart (19) has said:

> It may be stated that careful objective clinical assessment, based on previous experience with similar types of cases as a standard, should, with rigid safeguards, be adequate to demonstrate whether a new drug gives either benefit or no benefit, provided its action is more than slight. On the other hand, the inclusion of a matched control series, studied concurrently in order to permit comparisons having statistical validity, would seem im-

perative for a precise evaluation of a new drug's possibilities, limitations, and the degree of permanence of its benefit.

As has been pointed out, the need for concurrent controls has been recognized in this study and there has been random selection of cases on the four streptomycin regimens studied since April 1948 and, before that, to a certain degree on the other streptomycin regimens except in the case of the first one employed, the regimen of 1.8 or 2.0 Gm. a day for 120 days.

Presentation of results has nevertheless indicated that the selection of cases for treatment on different streptomycin regimens has not entirely reached the levels which are scientifically desirable. In the case of pulmonary tuberculosis, with relatively large numbers of cases, a considerable uniformity of clinical material, nevertheless, is present, certainly to a greater extent than in the case of various forms of extrapulmonary tuberculosis which have been investigated in this study and in which relatively smaller series were available.

The limitations of the methods of reporting results of the study to date have been mentioned. It is believed that, when detailed analysis of results is possible through the medium of the individual case report form recently initiated, many of the limitations of the data considered in this report will be removed and information along other important lines will be forthcoming. It is necessary at the present time to interpret the data which are available with the reservations indicated by these considerations.

With the increased number of cases studied and the increasing complexity of the study in general, the necessity for statistical evaluation has increased. This is particularly apparent in comparisons of results of treatment by several regimens. In Hart's words, streptomycin is no longer a "new drug", differences in its effect according to regimen are not "more than slight", and it does seem desirable to attempt a "precise evaluation of .... possibilities, limitations, and the degree of permanence of its benefit."

The "best" streptomycin regimen: It has not been the purpose of the study to define the single streptomycin regimen which is best suited to the treatment of all tuberculosis, or of any form of tuberculosis. This would be an obviously impossible and impractical undertaking at the present time. Emphasis has been placed on evaluation of such variations in streptomycin regimens as daily dose and duration of therapy.

The results presented have indicated with considerable statistical validity that, with respect to certain clinical observations in both pulmonary and extrapulmonary tuberculosis, streptomycin therapy of longer duration is superior to that of shorter duration; and, moreover, to a lesser extent, that a daily dose of 2.0 Gm. is superior to a daily dose of 1.0 Gm. In the latter instance, however, precise statistical analysis was required to detect this superiority, and the differences are slight even if statistically significant.

Moreover, it cannot be too strongly emphasized that slightly superior clinical results are only one part of the problem. Data have been presented which indicate conclusively that a streptomycin regimen of 2.0 Gm. a day is associated with much greater toxicity than one of 1.0 Gm. a day, especially if therapy is long

continued. It is as yet premature to expect that dihydrostreptomycin, or other derivatives of streptomycin which may yet be developed, will prove to be the entire solution to this problem. And the data for the rates of emergence of resistant organisms indicate conclusively that streptomycin administered daily for long periods of time, up to three or four months, and not in combination with other tuberculostatic drugs, results in an unfortunately high percentage of drug-resistant microorganisms.

The demonstrated degree of superiority of streptomycin regimens of greater duration and higher daily dosages, according to clinical observations, therefore, is of more theoretical than practical importance if the present limitations of toxicity and drug resistance remain unchanged. From the theoretical standpoint, there may be merit nonetheless in the recognition of these differences. Should, for example, a new derivative of streptomycin be developed which is markedly less toxic than streptomycin (or dihydrostreptomycin) and identical in therapeutic effect, it is probable that administration with larger daily doses would be advisable. And should devices be found which definitely reduce the rate of emergence of streptomycin-resistant tubercle bacilli on continuous daily therapy, as may be the case with combined streptomycin-PAS therapy, it is probable that courses of longer duration would be desirable. Another regimen with indications of great promise of maintaining therapeutic efficacy and delaying the emergence of drug resistance is that of administering streptomycin at intervals of approximately three days. It is possible that these two variations in therapy, combined chemotherapy and interrupted therapy, may themselves be combined to effect still further reduction of the limitations of drug fastness, and these possibilities are currently being investigated within this cooperative program. If, through such devices, the emergence of resistant strains of tubercle bacilli were to be further delayed, it is possible that it will be found desirable appreciably to lengthen the duration of such combined chemotherapy.

Summarizing this discussion of the relative merits of different streptomycin regimens in the treatment of tuberculosis, it may be said that the difference in clinical response between treatment with 2.0 Gm. a day and with 1.0 Gm. a day is very slight and of more theoretical than practical importance, particularly in view of the definitely greater toxicity of a regimen employing 2.0 Gm. a day. The difference in therapeutic response between treatment with 1.0 Gm. a day and with 0.5 Gm. a day is greater, the latter being definitely less effective, and there is not corresponding decrease in toxicity. In the light of these considerations *it is probable that 1.0 Gm. a day is the dosage of choice* of the three daily dosages investigated, all factors being considered.

With respect to continuous daily streptomycin therapy, although regimens of 42-day duration are found to be associated with less therapeutic response than their longer counterparts with equivalent dosages because of the importance of the limitation of drug resistance, it is nevertheless probable that duration of continuous therapy should generally not exceed 42 or 60 days. Addition of PAS, and such other devices as spacing administration of streptomycin farther apart, may modify this statement. It has not yet been demonstrated conclusively,

however, to what extent modifications will definitely delay drug resistance and retain therapeutic equivalence. Toxicity is a readily observed deterrent to the use of larger daily doses. The emergence of resistant strains of tubercle bacilli is not easily detected and is no less serious a deterrent to unwise use of streptomycin. Until regimens of combined therapy, or "interrupted" therapy, or both, have been standardized, therefore, the determination of the duration of streptomycin therapy should always keep in mind the limitation of emerging resistance. Relatively short courses of streptomycin therapy, in the range of 42 and 60 days, duration, with therapeutic efficacy approximating that of longer courses but with definitely less associated drug resistance, therefore at the present time appear to be the ones most appropriate for general use with deviations therefrom for special purposes only.

SUMMARY

1. Between July 1946 and April 1949, the cooperative investigation of the Veterans Administration, Army, and Navy has studied the effects of streptomycin in the treatment of approximately 4,500 cases of tuberculosis, including nearly 2,000 cases of pulmonary tuberculosis. Careful planning and effective liaison have resulted in uniform selection of clinical material and recording of results.

2. The clinical effects of seven different streptomycin regimens have been investigated, primarily with respect to the toxicity of the antibiotic, the rate of emergence of resistant strains of *M. tuberculosis*, and the therapeutic result. In addition, dihydrostreptomycin has been studied since December 1948.

3. It has been demonstrated that reducing the daily dosage of streptomycin from 2.0 Gm. to 1.0 Gm. to 0.5 Gm. has successively reduced the incidence of all important toxic manifestations; and that reducing the duration of administration of the drug from 120 days to 60 or to 42 days likewise is associated with reduced toxicity. A reduction of the number of injections into which the total daily dosage is divided has also been associated with decreased incidence of toxicity. These observations have been applied to vestibular dysfunction, impairment of renal function, dermatitis, drug pyrexia, and other toxic manifestations discussed in the text. Dihydrostreptomycin has been studied in only 56 cases, but it appears that it is less toxic than streptomycin with respect to vestibular function, but not otherwise significantly different in toxicity from its parent nonhydrogenated substance.

4. Strains of tubercle bacilli resistant to 10 γ per ml. or more of streptomycin emerge at a fairly regular rate, which appears to be independent of daily dosage in the ranges studied but definitely related to duration of therapy. At the end of 42 days of daily administration, approximately 35 per cent of specimens examined are resistant to 10 γ per ml. or more; at the end of 60 days, 50 per cent; at the end of 120 days, 75 per cent. Administration of streptomycin every third day instead of daily results in rates of emergence of resistant strains of approximately one-third of these figures. combined therapy, with para-aminosalicylic acid (PAS) added to streptomycin, reduces the rates of emergence of resistant strains still further.

5. Cases of pulmonary tuberculosis treated on seven streptomycin regimens, essentially homogeneous with respect to such criteria as stage of disease, pre-streptomycin course, and per cent cavernous and predominantly exudative, exhibited clinical results of considerable uniformity within the range of variables of regimen studied:

(a) Fever, when present at the start of treatment, was reduced in seven-eighths of the patients and reduced to normal in slightly over half. Three-eighths of the cases had a weight gain of over 10 pounds. The variations by regimen in these respects are not large.

(b) Roentgenographic improvement varies from 82 per cent in cases treated with 2.0 Gm. a day for 120 days, to 60 per cent in cases treated with 0.5 Gm. a day for 42 days. Among cases treated for 120 days, there is little decrease in the percentage showing all degrees of improvement, as the daily dose is decreased from 2.0 Gm. to 1.0 Gm. to 0.5 Gm., and to 1.0 Gm. every three days. There is more decrease in the percentage reported as exhibiting degrees of roentgenographic improvement defined as "marked" and "moderate." There is a significant decrease in the percentage of cases classified as "markedly and moderately" improved in each daily dosage category (2.0, 1.0, and 0.5 Gm. a day) when the duration of therapy is reduced from 120 to 60 or 42 days.

(c) Relapse rates are quite uniform for cases treated with larger total dosages and are slightly higher for cases treated with 1.0 Gm. a day for 42 days, or 0.5 Gm. a day for 120 or 42 days.

(d) Rates of "sputum conversion" by culture are remarkably uniform on all regimens studied, in spite of a considerable variation in the incidence of collapse therapy which was employed in the different groups.

(e) Mortality experience has been uniform for the cases treated on the regimens of higher total dosages; it is slightly greater for the cases treated for 42 days, as well as those treated with 0.5 Gm. a day for 120 days.

6. It has not been possible in cases of extrapulmonary tuberculosis to study the results of variations in streptomycin therapy with the same thoroughness as in the case of pulmonary tuberculosis, because of smaller numbers of cases and less complete data. To the extent that such an analysis is possible, however, the same trends with respect to variables of regimen are observed in these cases as in pulmonary tuberculosis.

7. The experience of the investigation in the treatment of miliary and meningeal tuberculosis, including a number of additional variations in therapy, has been presented. Whereas approximately 30 per cent of cases of miliary tuberculosis survive 18 months or more after the start of therapy, 10 per cent or less of cases which have tuberculous meningitis, whether with or without miliary tuberculosis, survive 18 months or more.

8. Primary emphasis has been placed in this report on the effect of variations in streptomycin regimen. Recognition has been given the complexity of the problem of the evaluation of results, including the statistical and the clinical. The investigation has probably raised as many questions as it has answered, and it is evident that the evaluation of streptomycin therapy in tuberculosis calls for the

careful balancing of many separate factors, especially those of toxicity, drug resistance, and the various facets of clinical response.

9. It is concluded that there has not yet been determined to be one "best" streptomycin regimen. One gram a day appears to be a satisfactory daily dosage, but the duration of therapy, the spacing of single administrations, and the combination with other chemotherapeutic agents with tuberculostatic properties such as PAS, have not yet been determined with validity. Because of the limitations imposed upon streptomycin therapy by the phenomenon of drug resistance, it is believed that duration of therapy should generally not exceed 42 or 60 days, until procedures designed for delaying the emergence of streptomycin-resistant strains of tubercle bacilli have been adequately standardized.

SUMARIO

Justipreciación de los Régimenes de Estreptomicina en el Tratamiento de la Tuberculosis. Reseña del Estudio Realizado por la Administración de Veteranos, el Ejército y la Marina de los E. U. A.

1. Entre julio, 1946 y abril, 1947, en una investigación cooperativa por la Administración de Veteranos, el Ejército y la Marina de los E. U. A., se han estudiado los efectos de la estreptomicina en el tratamiento de unos 4,500 casos de tuberculosis, incluso casi 2,000 de la forma pulmonar. Un planeamiento cuidadoso y una colaboración efectiva han dado por resultado uniformidad en la selección de los casos y en la anotación de resultados.

2. Fueron investigados los efectos clínicos de siete distintos régimenes de estreptomicina, primordialmente con respecto a la toxicidad del antibiótico, el coeficiente de aparición de cepas resistentes del *M. tuberculosis* y el resultado terapéutico. Además, se ha estudiado la dihidroestreptomicina desde diciembre, 1948.

3. Queda demostrado que, rebajando la dosis diaria de estreptomicina de 2.0 Gm. a 1.0 Gm. y a 0.5 Gm., se ha reducido sucesivamente la incidencia de todas las importantes manifestaciones tóxicas; y que disminuyendo la duración de la administración de la droga de 120 a 60 ó 42 días, también se atenúa la toxicidad. Una reducción del número de inyecciones en las cuales se divide la dosis diaria total ha ido igualmente asociada con menor toxicidad. Estas observaciones rezan con la disfunción vestibular, el deterioro de la función renal, la dermatitis, la pirexia medicamentosa y las otras manifestaciones tóxicas discutidas en el texto del trabajo. La dihidroestreptomicina solo fué estudiada en 56 casos, pero parece ser menos tóxica que la estreptomicina con respecto a la función vestibular, aunque en lo demás no discrepar mayor cosa de la sustancia matriz no hidrogenada.

4. Cepas de bacilos tuberculosos resistentes a 10 γ por ml. o más de estreptomicina aparecen con bastante regularidad, lo cual parece ser independiente de la dosis diaria dentro de los límites estudiados pero estar claramente relacionado don la duración de la terapéutica. Al cabo de 42 días de administración diaria, aproximadamente 35 por ciento de los ejemplares examinados son resistentes a

γ por ml. o más; al cabo de 60 días, 50 por ciento; al cabo de 120 días, 75 por ciento. La administración de estreptomicina cada tres días, en vez de cada día, hace bajar a la tercera parte esas cifras de aparición de cepas resistentes. La terapéutica combinada, con el ácido para-aminosalicílico (PAS) agregado a la estreptomicina, hace bajar todavía más los coeficientes de aparición de cepas resistentes.

5. Los casos de tuberculosis pulmonar tratados con siete régimenes de estreptomicina, esencialmente homogéneos con respecto a pautas tales como período de la enfermedad, tanda de preestreptomicina y por ciento de formas cavernosas y de predominio exudativo, manifestaron resultados clínicos de considerable uniformidad, dentro de la variabilidad de los régimenes estudiados.

(a) La fiebre, cuando existía al iniciar el tratamiento, bajó en siete octavos de los enfermos y descendió a lo normal en poco más de la mitad. En tres octavas partes de los casos hubo un aumento de peso de más de 4.5 kg. Las variaciones conforme al régimen seguido no fueron importantes en esos sentidos.

(b) La mejoría radiológica varió de 82 por ciento en los casos tratados con 2.0 Gm. diarios por 120 días, a 60 por ciento en los tratados con 0.5 Gm. diarios durante 42 días. Entre los tratados durante 120 días, disminuyó poco el porcentaje que muestra los distintos grados de mejoría, a medida que la dosis diaria disminuyó de 2.0 Gm. a 1.0 Gm. y 0.5 Gm., y a 1.0 Gm. cada tres días; bajó más el porcentaje que muestra los grados de mejoría radiológica rotulados como "marcada" y "moderada". Hubo una disminución significativa en el porcentaje de casos clasificados como "marcadamente" y "moderadamente" mejorados en cada categoría posológica diaria (2.0, 1.0 y 0.5 Gm. diarios) cuando la duración de la terapéutica fué disminuída de 120 a 60 ó 42 días.

(c) Los coeficientes de recidivas fueron bastante uniformes para los casos tratados con dosis totales mayores y algo más altos para los tratados con 1.0 Gm. diario durante 42 días o 0.5 Gm. diarios durante 120 ó 42 días.

(d) Las tasas de viraje del esputo en los cultivos fueron notables por lo uniformes con todos los régimenes estudiados, a pesar de la considerable variación en la incidencia de colapsoterapias empleadas en los distintos grupos.

(e) La mortalidad experimentada fué uniforme en los casos tratados con los régimenes más altos en dosis total; levemente mayor en los tratados durante 42 días así como en los tratados con 0.5 Gm. diarios durante 120 días.

6. En los casos de tuberculosis extrapulmonar no fué posible estudiar los resultados de las variaciones de la estreptomicinoterapia con la misma minuciosidad que en los de tuberculosis pulmonar, debido a ser más pequeño el número de casos y menos completos los datos. Sin embargo, hasta donde fué posible observar, rigieron las mismas tendencias con respecto a las variaciones de régimen que hubo en la tuberculosis pulmonar.

7. Preséntanse los datos relativos al tratamiento de la granulia y la tuberculosis meníngea, comprendiendo varias alteraciones más de la terapéutica. En tanto que sobreviven unos 30 por ciento de los casos de granulia 18 meses o más después de iniciar la terapéutica, sólo sobreviven ese tiempo 10 por ciento o menos de los que tienen meningitis tuberculosa (ya haya o no granulia).

8. En esta memoria se ha hecho hincapié en particular en el efecto de las variaciones del régimen de estreptomicina, reconociendo lo complejo que es el problema de la valuación de los resultados, incluso los estadísticos y los clínicos. La investigación probablemente ha planteado tantos problemas como los que ha resuelto, siendo manifiesto que la justipreciación de la estreptomicinoterapia en la tuberculosis exige el delicado balanceo de muchos factores separados, y en particular los de toxicidad, farmacorresistencia, y las varias facetas de la respuesta clínica.

9. Dedúcese que no se ha determinado todavía que haya un régimen estreptomicínico "mejor". Un gramo diario parece constituir una dosis diaria satisfactoria, pero la duración de la terapéutica, el espaciamiento entre las administraciones y la combinación con otros agentes quimioterápicos dotados de propiedades tuberculoestáticas, son puntos que no han sido aun determinados positivamente. Por virtud de las limitaciones impuestas a la estreptomicinoterapia por el fenómeno de farmacorresistencia, parece que la duración del tratamiento no debe generalmente exceder de 42 ó 62 días, hasta que se hayan normalizado en forma adecuada los procedimientos encaminados a retardar la aparición de cepas estreptomicinorresistentes de bacilos tuberculosos.

Acknowledgment

It is impossible to acknowledge the assistance of the many individuals who have assisted in the preparation of this paper. In addition to the hundreds of individual investigators whose data have been used, the author is indebted to many who have criticized the analysis and the presentation in manuscript form. He is particularly indebted to Dr. Nicholas D. D'Esopo, Chief, Medical Service, VAH, Sunmount, New York; Dr. W. Spencer Schwartz, Chief, Professional Services, VAH, Oteen, North Carolina; Mr. William Steenken, Trudeau Sanatorium, Saranac Lake, New York; and to Dr. Arthur M. Walker, Secretary, Streptomycin Committee, Veterans Administration, Washington, D. C., for helpful criticisms and suggestions.

REFERENCES

(1) Streptomycin Committee, Central Office, Veterans Administration: The effect of streptomycin upon pulmonary tuberculosis: Preliminary report of a cooperative study of 223 patients by Army, Navy, and Veterans Administration, Am. Rev. Tuberc., 1947, *56*, 485.

(2) Streptomycin Committee: The effects of streptomycin on tuberculosis in man, report to the Council on Pharmacy and Chemistry, J.A.M.A., 1947, *135*, 634.

(3) Streptomycin Committee: Streptomycin in the treatment of tuberculosis: Current status, report to the Council on Pharmacy and Chemistry, J.A.M.A., 1948, *138*, 584.

(4) Minutes of the Fourth Streptomycin Conference, October 9–12, 1947, St. Louis, Mo., published by Veterans Administration Branch Office No. 9, Tuberculosis Section, St. Louis, Mo.

(5) Minutes of the Fifth Streptomycin Conference, April 15–18, 1948, Chicago, Illinois, published by Veterans Administration Branch Office No. 7, Tuberculosis Section, Chicago, Ill.

(6) Minutes of the Sixth Streptomycin Conference, October 21–24, 1948, St. Paul, Minn., edited by Veterans Administration Branch Office No. 8, Tuberculosis Section, St. Paul, Minn.

(7) Minutes of the Seventh Streptomycin Conference, April 21–24, 1949, Denver, Colo., edited by Veterans Administration Area Office, Tuberculosis Section, Washington, D. C.

(8) Mason, E. E., Crouch, W. H., Kridelbough, W. W., and Ward, M.: Streptomycin in the treatment of tuberculous enteritis, Am. J. M. Sc., 1949, *217*, 28.

(9) Brown, T. McP., and Wichelhausen, R. H.: Tuberculous peritonitis treated with streptomycin: a report on 26 cases, Am. J. Med. (to be published).

(10) Ebert, R. V., and Falk, A.: Streptomycin in the treatment of tuberculous pericarditis (in preparation).

(11) Titche, L. L.: Streptomycin in the treatment of tuberculosis of the ear (in preparation).

(12) Michael, M.: Streptomycin in the treatment of tuberculosis of the skin (in preparation).

(13) Parisi, P. J.: Streptomycin in the treatment of tuberculosis of the eye (in preparation).

(14) Moyer, R. E.: The value of different regimens in the treatment of tuberculous sinuses, Minutes of the Seventh Streptomycin Conference, April 21–24, 1949, Denver, Colo. (7).

(15) Lattimer, J. K., Amberson, J. B., Jr., and Braham, S.: The treatment of genitourinary tuberculosis with streptomycin alone, J. Urol. (to be published).

(16) Results of Jury Review of Streptomycin-treated Cases of Tuberculosis of Bones and Joints, distributed in mimeographed form to Study Units, March 1948.

(17) Bunn, P. A.: One hundred cases of miliary and meningeal tuberculosis treated with streptomycin, Am. J. M. Sc., 1948, *216*, 286.

(18) Bunn, P. A.: The two-year follow-up of patients with miliary and meningeal tuberculosis treated with streptomycin, Am. J. M. Sc. (to be published).

(19) Hart, P. D.: Chemotherapeutic measures in tuberculosis: General assessment and current problems, Am. Rev. Tuberc., 1949, *59*, 223.

DIFFUSE PULMONARY GRANULOMATOSIS IN YOUNG WOMEN FOLLOWING EXPOSURE TO BERYLLIUM COMPOUNDS IN THE MANUFACTURE OF RADIO TUBES

Report of Five Cases

PAUL SLAVIN[1]

(Received for publication April 20, 1949)

INTRODUCTION

Five young women, with a history of employment in the manufacture of radio tubes, developed a chronic lung ailment characterized by shortness of breath, cough, high pulse rate, and weight loss. Increasing difficulty in breathing appeared to be the main disabling feature. The illness came on insidiously and the patients became aware of it when they no longer were employed in the radio tube factories.

In the first case no definite ante-mortem diagnosis was made and the nature of the disease became apparent through the autopsy findings. The patient died in May 1944, at a time when a group of workers in a fluorescent lamp factory, Salem, Massachusetts, developed an occupational lung illness. The autopsy material obtained in this case by Dr. Harrison S. Martland was forwarded by him to the late Dr. L. U. Gardner, Saranac Lake, for correlation with the findings in the Salem cases. Beryllium and other components of phosphors were revealed in a specimen of her lungs. Later on, the Kettering Laboratory reported 3.0 γ of beryllium in 100 Gm. of wet lung tissue. Part of the pathological report by Dr. Gardner and also the chemical and spectrographic analyses are included in the presentation of this case.

Three patients are alive. One of them had been working for over eight years in three different radio tube plants, in each of which she had been exposed to dust inhalation.

The other 2 patients had been employed for several years in the same plant, where the second patient spent her last fourteen months of factory employment. They had been working in the spray room, where the cathodes, grid hooks, and filaments of the tubes are being coated with a mixture of phosphors.

The fifth case is included in retrospect. She was seen in 1935 and no significance was attached then to her history of employment in a radio tube plant. The diagnosis could not be determined clinically and no autopsy was obtained.

CASE REPORTS

Case 1: The patient, C. D., was a 25-year-old, married, white woman. She was first seen on October 29, 1942, when she consulted the writer because of severe shortness of breath.

Difficulty in breathing and a mild cough had begun about one year previously. She became irritable and unduly fatigued at work. She consulted her family physician in December 1941 and on January 3, 1942 her illness was diagnosed as rheumatic heart disease and

[1] 31 Lincoln Park, Newark, New Jersey.

she was advised to give up working and to limit her activities at home. However, medication and rest from work brought ne relief. Early in October 1942, while out for a walk, she felt a sudden sharp pain in the chest and became very short of breath. Her temperature had apparently remained normal since the beginning of the sickness. No sputum examinations or chest roentgenograms had been obtained.

The past history was noncontributory, except for an illness in 1938 from May until July when her knees and ankles became swollen and red blotches appeared on her legs. The illness was considered to be rheumatic in nature. The family history was negative for tuberculosis and for rheumatic fever.

The patient began to work in factories at the age of seventeen. In 1934 and 1935 she worked for fourteen months on radio tubes in two different factories. In January 1937 she obtained employment in a plant for the manufacture of telephone equipment. The patient was engaged mainly in removing insulation from copper wires by means of revolving steel wire brushes. Some of the copper wires were made of an alloy containing beryllium. She was not protected against inhaling the dust scattered by the brushes. During 1938 and 1939 she was unemployed and in 1940 resumed the work of removing insulation from copper wires and continued until January 1942, when she became disabled.

The patient was a small, undernourished woman. Her breathing was rapid and shallow. The visible mucous membranes were cyanotic. The fingers were slightly clubbed. The superficial regional lymph nodes were not enlarged. There was no evidence of edema or skin lesions. The pulse was rapid, small and regular. The heart sounds were clear with accentuation of the second pulmonic sound. The liver and spleen were not enlarged.

A chest roentgenogram (figure 1, October 29, 1942) showed that the right lung was collapsed by a pneumothorax occupying the outer one-third of the field. The visible portion of the lung was diffusely infiltrated with nodules. The apex of the upper lobe contained a rarefied area, connected by slender adhesions with the dome of the chest wall. A massive density, apparently representing enlarged tracheobronchial lymph nodes, was present in the root region. The right hemidiaphragm was depressed to a level lower than the left leaf. The costophrenic sinus was clear. The left lung was also diffusely infiltrated with nodules and only its outer basal portion was hyperaerated and did not clearly show the infiltration. The heart was displaced to the left and presented a marked bulge in the region of the pulmonary conus. The bulge was evidently formed by merging shadows of an enlarged right ventricle and of enlarged tracheobronchial lymph nodes.

Four weeks later, following bed rest at home, her chest roentgenogram (figure 2, November 27, 1942) showed the right lung fully re-expanded, with no definite cavity visualized in its upper lobe. Both lung fields were packed with nodular densities, irregular in shape and varying in size from 1 mm. to 1 cm. These large nodules were superimposed on a background stippled with discrete miliary nodules. Minute calcific deposits were visualized in occasional nodules. The apical and costophrenic regions of both lungs contained areas of increased translucency. The horizontal interlobar septum was elevated to the second anterior intercostal space. The right hemidiaphragm rose to a level higher than the left and appeared to be tented. The heart returned to a normal position. The bulge in the region of the pulmonary conus remained unchanged.

Repeated sputum examinations were negative for tubercle bacilli and for fungi. Skin tuberculin tests were also negative.

In the latter part of February 1943, the patient suddenly began gasping for breath and became extremely cyanotic. Physical examination revealed recurrence of the right-sided spontaneous pneumothorax. Oxygen had to be administered intermittently for three to four hours daily.

A chest roentgenogram of April 3, 1943 still showed a residual pneumothorax along the upper outer margin of the right lung.

On April 25, 1943 the patient entered a hospital for observation. No definite diagnosis was made. The right lung was again re-expanded and there was no evidence of a pleural effusion. Oxygen inhalation was discontinued during the last two days of hospitalization.

She returned home on May 6, 1943 and two days later the right lung ruptured spontaneously for the third time. Oxygen inhalation was administered constantly day and night (4 to 5 tankfuls weekly) from this time until her death twelve months later.

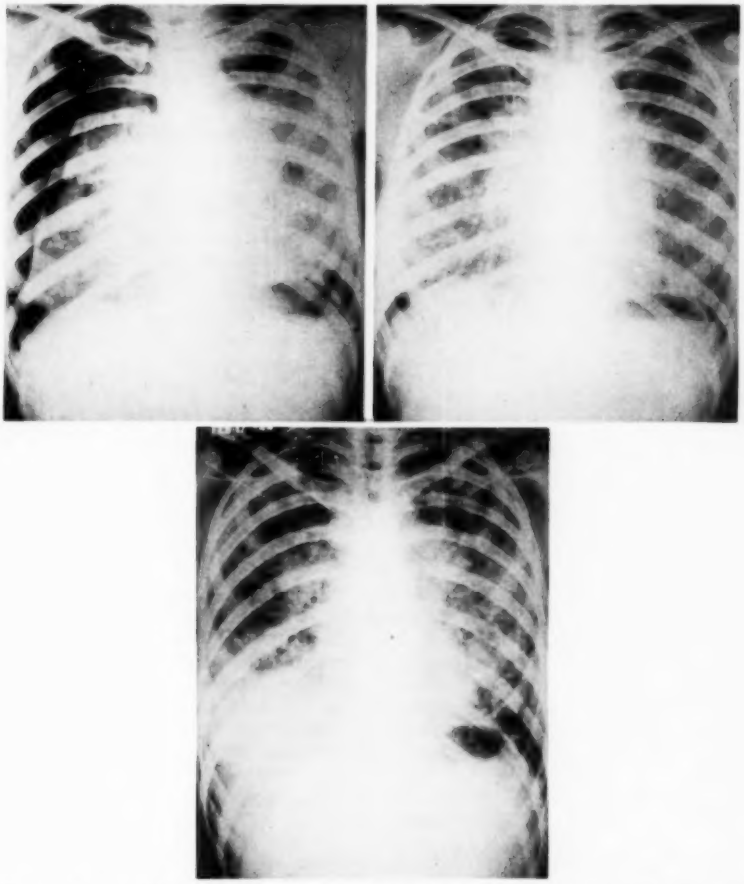


FIG. 1. Case 1. (Upper left) October 29, 1942. Right-sided spontaneous pneumothorax Diffuse nodular infiltration. Enlarged tracheobronchial lymph nodes. Cor pulmonale.

FIG. 2. Case 1. (Upper right) November 27, 1942. Right lung re-expanded

FIG. 3. Case 1. (Bottom) February 17, 1944. Pattern of nodular infiltration unchanged. Pleural effusion simulating elevated right diaphragm.

A chest roentgenogram of September 13, 1943 showed a pleural effusion at the base of the right lung.

The last chest roentgenogram (figure 3, February 17, 1944) revealed a convex configuration of the basal pleural effusion which simulated an elevated right diaphragm. Areas of

increased translucency were present in the apices of both lungs and in the left costophrenic sinus. The nodular infiltration remained unchanged.

Roentgenographic examination of the bones of both hands was negative.

The temperature continued virtually normal during the entire course of the illness. There was no evidence of the presence of an acute inflammatory process. Her weight came down to 72 pounds, a loss of 38 pounds as compared with her highest weight. The menstrual periods were absent for several months. She remained mentally alert and, although continuously under an oxygen mask, managed to do reading and hand sewing.

On May 8, 1944 early in the morning, she asked to be propped up, stating that she was no longer able to breathe. She died a few minutes later.

POST-MORTEM EXAMINATION BY DR. HARRISON S. MARTLAND, MAY 8, 1944

The fingernails were distinctly clubbed. There were no palpable lymph nodes or skin lesions. One pint of straw-colored fluid was found in the abdominal cavity and pelvis. The liver was displaced and extended three finger-breadths below costal margin. The diaphragm was opposite the sixth rib on the right side and the fifth rib on the left side.

One pint of straw-colored fluid and a few old adhesions were present in the right pleural cavity. There were a few old adhesions over the apex of the left lung. The pericardial cavity contained 50 cc. of clear yellow fluid. There was marked hypertrophy of the right ventricle, the muscle in the conus being 9 mm. thick. There was no hypertrophy of the muscle of the left ventricle which was only 6 to 7 mm. in thickness. No rheumatic lesions were present on any of the valves. Near the cardiac end of the stomach there was one large node, 3 cm. in diameter, which revealed on section the same appearance as the hilar nodes. The liver was small with distinct nutmeg markings. No granulomatous lesions were found.

REPORT BY DR. LEROY U. GARDNER, DECEMBER 1, 1944

Gross Appearance of Fixed Tissues Submitted: The pleural surfaces of the right lung were roughened, due to the presence of tags of fibrous adhesions between which were occasional thin-walled blebs projecting above the surface.

The specimen included portions of the upper and middle lobes only. The major part of the former and that part of the middle adjacent to the interlobar fissure were consolidated and contained relatively few patent air spaces. Inspection with a lens revealed numerous discrete, grey nodules which were rarely larger than 1 mm. in diameter. These in every way resembled small silicotic lesions. Between them the walls of air spaces were generally thickened, so that the alveoli were greatly reduced in size. Some of this interstitial fibrosis was also nodular in character, but such lesions lacked the definition of the previously described "silicotic" type foci, being much smaller, yellow in color, and without dust pigmentation.

Extending downward from the apex was a multilocular cavity with trabeculation due to undestroyed vessels and other band-like structures. On the trabeculae were many minute, yellowish nodules. This cavity, which extended within 3 mm. of the pleura, had no definite walls and showed no evidence of caseation. The surrounding tissue was either air-containing or in places consisted of conglomerations of grey pigmented nodules.

The middle lobe presented widespread coarse emphysema with intercommunicating blebs as large as 1 cm. in diameter. This change was largely central in the slab of tissue submitted. The margins of the lobe contained more air, but even here a lens revealed thickened alveolar walls with many small colorless and scattered larger, discrete, grey nodules.

Vessels and bronchi were not remarkable. The bronchial nodes were enlarged, moderately firm, grey, mottled with yellow. The normal architecture was largely obscured. The surrounding connective tissue was not disturbed.

Examination of the left lung showed a picture similar to that of the right, with the exception of the cavity. There were more and larger discrete nodules of the "silicotic" type in the apex of the upper lobe and many more of the minute, ill-defined, yellow nodules

throughout the lung. Coarse emphysema was largely confined to the lower lobe and extended to the diaphragmatic surface. The lymph nodes on this side were larger than those on the right but were of the same general appearance. Individual units measured as much as 2 cm. in diameter.

Microscopic: The lungs showed a widespread interstitial granulomatous reaction which consisted of nodules of microscopic dimensions and some more diffuse changes plus large hyaline nodule formation, coarse emphysema, chronic pleurisy, and thickened interlobar septa. Very little dust was visible.

The minute granulomas had all the characteristics of sarcoid and showed various phases of reaction from early focal prohferation of mononuclear and giant cells to advanced hyaline sclerosis. Evidence of caseation or other forms of necrosis was lacking. The fibrous elements of these granulomas were concentrically arranged about the giant cells. Not infrequently the more peripheral fibers had undergone hyaline degeneration and in some instances such changes involved the entire nodule. Infiltration with lymphoid cells was more prominent than in many cases.

Giant cells were very numerous and they frequently contained inclusion bodies which stained black with hematoxylin and reacted for iron with acid ferrocyanide, but not for calcium. These bodies were unusually large, irregular in shape, and did not polarize light. Some consisted of rounded conchoidal masses, others were elongated spicules with various-shaped dilatations. Still others consisted of granular deposits upon the surface of crystal clefts. Visible particulate dust was minimal in amount.

More diffuse reactions of a similar character involved localized portions of the interstitial tissue at the periphery of the lung. Here the air spaces were compressed by very marked thickening of the alveolar walls and other interstitial tissues. Instead of nodules there were scattered giant cells embedded in connective tissue, which varied from cellular to hyaline type, with a heavy infiltration of lymphoid cells. In these locations the strands of hyaline fibers suggested amyloid formation. The thickening of the pleura and septa between secondary lobules was due to such reaction, with both discrete nodules and heavy fibrous tissue participating.

The *large hyaline nodules*, readily visible on gross inspection of the section, appeared very much like silicotic lesions. They were sharply defined, often occurred in clusters, and were then surrounded by a common capsule which was likewise composed of hyaline fibers and stained less intensely with eosin than the enclosed smaller unit nodules. The latter consisted of concentric laminae of hyaline fibers. Unlike most silicotic nodules they showed no trace of compressed nuclei. They contained very little visible dust and there was an unusually abrupt transition between the hyaline zone and the mononuclear cellular zone at the periphery. In the mature silicotic nodule the hyaline center was surrounded by thinner, well-separated fibers with few mononuclear cells remaining at this stage. Furthermore, while the hyaline in this case had a fibrous structure, the component elements appeared to have undergone partial autolysis, so that their outlines were somewhat obscured.

The change was different from the granular degeneration that occurs when a silicotic nodule is complicated by tuberculosis.

In a few areas there was partial calcification within these large hyaline nodules. The lime salts were deposited either as clusters of minute granules or about strands of fiber suggesting elastic tissue. The presence of calcium was confirmed by Von Kossa stain.

The cavity described in the gross examination had none of the characteristics of a tuberculous antrum, no caseation, no exudate or necrotic debris in its walls, and very little adherent to the inner surface. It seemed to consist simply of an irregular opening in the pathological tissues with no organized wall. Sarcoid nodules, cellular or hyaline, unaltered blood vessels, et cetera, directly abut upon the opening with no intervening membrane. At least in two sections taken, there was no communication with a bronchus. The trabeculae noted in the gross examination consisted of hyaline nodules, perhaps strung upon a blood vessel. Calcified foci were particularly frequent both on the surface and in the interior of nodules abutting on this cavity.

The bronchi and bronchioles appeared quite normal except for distortion by surrounding lesions and an excess of mucus in goblet cells and in some places in the lumina. The epithelium of the smaller air spaces had become cuboidal, where backed by proliferative lesions.

The blood vessel changes consisted of an obliteration of the capillary bed with the persistence of large thin-walled arterioles in the newly formed tissue and a moderate to marked degree of endarteritis in many but not all vessels of larger calibre. None were found in which complete obliteration of the lumen had occurred.

The *tracheobronchial nodes* were unusually large and most of their normal architecture had been replaced by lesions similar to those in the lungs. Conglomerate, hyaline fibrosis had completely replaced the central portion of most nodes, leaving only a thin rim of lymphoid tissue at the periphery. The latter was seeded with small granulomas, either cellular or in various stages of hyaline degeneration. Visible dust was small in amount, but inclusion bodies occurred in the peripheral zone and occasionally within the large central hyaline mass.

Chemical analysis revealed the following values:

Zn	Be	Mn	SiO_2	Mg	W
0.20 per cent	*N. F.	**F. T.	4.36 per cent	2.78 per cent	Zero

* N.F.—None found.
**F.T.—Faint Trace.

Spectrographic analysis revealed the following values:

Zn	Be	Mn	SiO_2	Mg	W
25	5	10	50	60	Zero

Case 2: The patient, S. K., was a 35-year-old, married, white woman who was first seen by the writer on September 19, 1946.

Her present illness began seven years previously, in August 1939, nineteen months after she had stopped working on radio tubes. Since that time she had been complaining of shortness of breath, productive cough, and weight loss. Repeated examinations in a tuberculosis clinic did not determine the nature of her illness. Sputum tests were negative for tubercle bacilli and for fungi. Skin tuberculin tests were also negative. An operation on her sinuses in 1943 and a tonsillectomy in 1945 brought no relief. A roentgenographic diagnosis of sarcoidosis was made in February 1944.

The history of past diseases was noncontributory. She gave birth to two children. The first was born in September 1938, eight months after she quit factory work. The second child was born in November 1945, six years after the beginning of her present illness. Both deliveries were under spinal anaesthesia.

The patient's father died of pulmonary tuberculosis at the age of 52.

The patient began to work in factories at the age of thirteen. At sixteen she worked for eight months on radio tubes. At nineteen she resumed this work and continued for seven and one-half years in two different plants, from 1930 until January 1938. Her work included mounting radio tubes, welding parts of the tubes, welding carbon plates to tubes, mounting grids, and finally handling mica plates for fourteen months. Her employment in places other than radio tube factories involved no occupational exposure.

She was undernourished, having lost 34 pounds from a high of 160 pounds. Her breathing was rapid and the visible mucous membranes were slightly cyanotic. The fingers were not clubbed. There was no evidence of skin lesions and the superficial regional lymph nodes were not enlarged. The heart sounds were clear. Adventitious sounds were present over the upper lobes of both lungs and at the base of the right lung. The liver and spleen were not

palpable. The blood pressure was 104 mm. of mercury systolic and 82 mm. diastolic. The vital capacity was 1,000 cc.

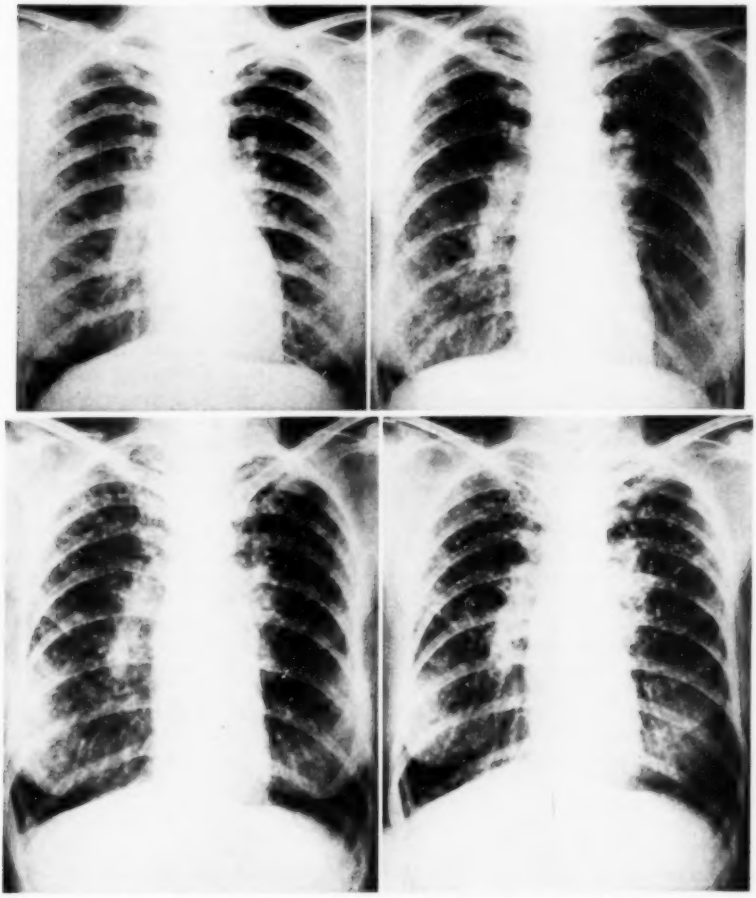


FIG. 4. Case 2. (Upper left) November 8, 1939. Diffuse granular infiltration. Hilar shadows increased in size and density. Heart normal.

FIG. 5. Case 2. (Upper right) January 25, 1944. Diffuse reticulonodular infiltration, overshadowing the original granular nodulation.

FIG. 6. Case 2. (Lower left) February 2, 1949. Disseminated calcification of nodules. Reticulonodular pattern unchanged.

FIG. 7. Case 2. (Lower right) June 19, 1949. Increased calcification of nodules. Tuberculin and histoplasmin skin tests negative. Heart normal.

Her first chest roentgenogram (figure 4, November 8, 1939) showed a diffuse granular infiltration through both lungs. Occasional larger nodules were present among the minute

granules and alongside the vascular markings. The hilar shadows were enlarged and of increased density. The heart shadow was of a normal configuration.

Subsequent chest roentgenograms showed a steadily developing reticulonodular pattern of infiltration, overshadowing the granular nodulation.

A chest roentgenogram, taken four years later (figure 5, January 25, 1944) showed a diffuse reticulonodular infiltration through both lungs. The network was composed of nodular densities and fibrous tissue strands. The background was diffusely stippled with discrete punctate nodules. Calcific deposits were present within some of the larger nodular densities. The tracheobronchial lymph nodes showed no further enlargement. The heart shadow was unchanged.

The chest roentgenograms of October 18, 1944, September 19, 1946, and February 2, 1948 revealed spreading calcification of the nodules.

In January 1949, she missed a menstrual period and in February her urine pregnancy test was positive. She complained of further weight loss and of increasing weakness. Her cough and expectoration were aggravated by the cold weather. The shortness of breath remained unchanged.

The chest roentgenogram (figure 6, February 2, 1949) showed widespread calcification through both lungs, the calcific deposits being embedded within the larger nodular densities. The reticulonodular pattern of infiltration remained unchanged. Miliary granules were still visualized in the background, but most of them were obscured by connective tissue infiltrates and by rarefied areas, representing coarse emphysema and blebs. The right costophrenic sinus was blunted. The heart shadow appeared to be narrower.

There was no evidence of continuing invasiveness. The granulomatous reaction was apparently in its final stage of evolution, the stage of stabilized calcifying lesions.

A therapeutic abortion was advised and performed. Foci of necrosis were present in the placenta.

The last examination on June 19, 1949 revealed some improvement in her general condition. With the passing of the cold weather, her cough and expectoration had decreased and she had gained four pounds in weight. The pulse rate was 86 per minute. The heart sounds were normal. Only occasional adventitious sounds were heard over the lungs. The vital capacity was 1,675 cc., as compared with 1,000 cc. during the winter months. The test, repeated twice, weakened her and ten minutes later her blood pressure was 80 mm. of mercury systolic and 72 mm. diastolic. In another ten minutes, readings of 92 mm. systolic and 72 mm. diastolic were obtained.

The chest roentgenogram (figure 7, June 19, 1949) showed additional calcific deposits within the larger nodules. More miliary granulomas became obscured by connective tissue proliferation. The heart shadow appeared to be normal. The hilar shadows were of increased density.

The histoplasmin skin test (1:100 dilution) was negative.

Case 3: The patient, N. Y., was a 29-year-old, married, white woman who was first seen on June 19, 1948.

In 1945, while still working on radio tubes, she developed shortness of breath on dancing and on climbing. She also began to lose weight. She attributed these changes to married life. In January 1947, six months after she stopped working in the radio tube factory, she developed a productive cough. She was treated for an upper respiratory infection but failed to improve. Her condition grew worse after she became pregnant about one month later. The roentgenographic findings in May 1947 were interpreted as a recent pulmonary infection of unknown origin and she was hospitalized as a pneumonia case. On November 8, 1947, the patient gave birth to her first child. The shortness of breath and cough grew steadily worse. Repeated roentgenographic examinations continued to reveal an obscure pulmonary infection, which showed clearing immediately after childbirth but became aggravated later on. Tubercle bacilli could not be demonstrated in her sputum. The skin

tuberculin tests were reported negative. On June 15, 1948 her illness was diagnosed as possible beryllium granulomatosis.

The history of past diseases was noncontributory.

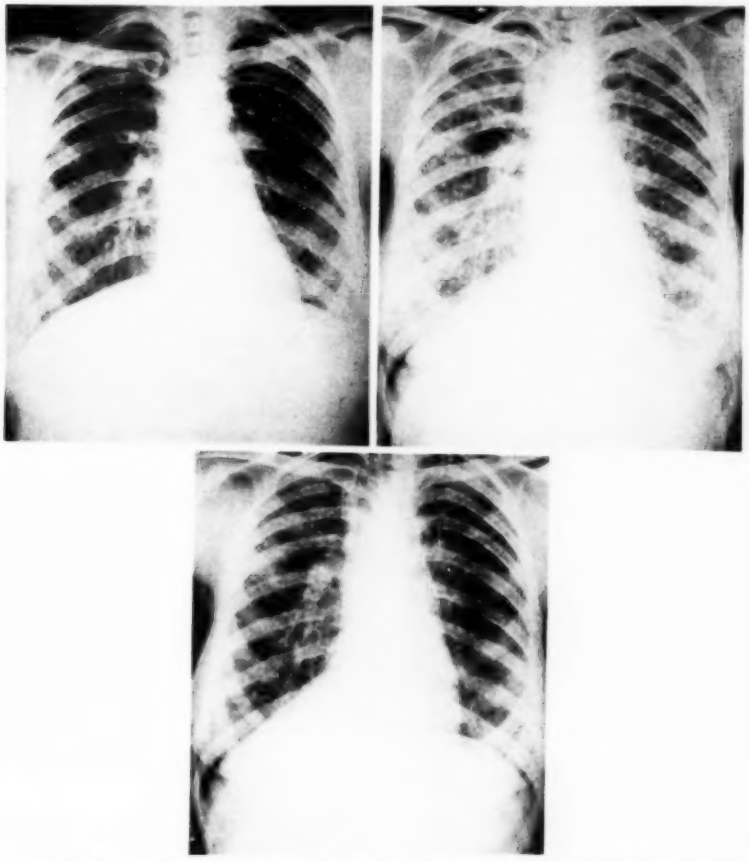


FIG. 8. Case 3. (Upper left) July 14, 1947. Diffuse reticulonodular infiltration. Left border of heart straightened.

FIG. 9. Case 3. (Upper right) November 16, 1948. Increased reticulonodular infiltration. Right diaphragm elevated. Bulge in pulmonary conus.

FIG. 10. Case 3. (Bottom) June 18, 1949. Reticulonodular pattern unchanged. Cor pulmonale.

The family history was negative for pulmonary tuberculosis.

The patient began to work at the age of fourteen. At twenty she worked for eight months on radio tubes. From August 1938 until June 1946, she had been employed continuously in the same radio tube factory where the second patient (Case 2) spent her last fourteen

months of employment. There, for the first year the present patient was engaged in soldering caps on radio tubes and the remaining seven years she spent in the spray room, spraying grid hooks for two years and cathodes for the next five years. Her employment in places other than the radio tube factories involved no occupational exposure.

The physical examination revealed shortness of breath and cyanosis of the visible mucous membranes. The superficial regional lymph nodes were not enlarged and there were no skin lesions. The fingers were not clubbed. The pulse rate was 86 per minute. The heart sounds were clear, the second pulmonic sound was accentuated. Adventitious sounds were present over the right lung anteriorly and over the left lower axillary region. The liver and spleen were not palpable. The blood pressure was 112 mm. of mercury systolic and 78 mm. diastolic. The vital capacity was 1,600 cc., or 50 per cent of the normal. The weight was normal, 10 pounds less than her highest weight.

Her previous chest roentgenogram (figure 8, July 14, 1947) showed a generalized reticulonodular infiltration through both lung fields. The nodules together with fibrous tissue strands formed a dense network, the background of which was stippled by a diffuse miliary nodulation. The hilar shadows were of increased density. The left border of the heart shadow was straightened.

The skin tuberculin test was positive.

Examination on November 16, 1948 revealed a lowering of her vital capacity to 1,200 cc. The chest roentgenogram (figure 9, November 16, 1948) showed increased nodulation in both lungs. The reticulonodular pattern of infiltration remained unchanged. On the right, linear areas of atelectasis were present in the lower lateral portion of the lung and the diaphragm was elevated, causing the nodules to become more crowded than on the left side. The hilar shadows were increased in size and the bronchovascular markings extending into the bases were thickened. There was now a bulge in the region of the pulmonary conus.

The granulomatous reaction was obviously still in the invasive stage.

The last examination on June 18, 1949 revealed some improvement in her general condition. Her cough and expectoration subsided with the coming of warm weather. She had gained three pounds in weight. Her pulse rate was 100 per minute. Only occasional adventitious sounds were heard over either lung. The second pulmonic sound was markedly accentuated. The blood pressure was 104 mm. systolic and 72 mm. diastolic. The vital capacity was 1,500 cc., as compared with 1,200 cc. in November 1948. The test provoked coughing and could not be repeated.

The chest roentgenogram (figure 10, June 18, 1949) showed no increase in the nodulation and no change in the reticulonodular pattern of infiltration. On the right, the linear areas of atelectasis were still present in the lower portion of the lung and the diaphragm remained elevated. The bulge in the region of the pulmonary conus became more prominent.

There was no evidence of continuing invasiveness, but the outlook was unfavorable because of advancing right ventricular enlargement.

Case 4: The patient, F. D., was a 26-year-old, unmarried, white woman who was first seen on June 21, 1948.

In February 1948, fifteen months after she had stopped working in a radio tube factory, the patient noticed some shortness of breath on climbing and became aware of weight loss. In April 1948 she developed a cough and began to raise "lumpy sputum." On June 7, 1948 she consulted her family physician who advised a chest roentgenogram and interpreted the findings as indicative of beryllium granulomatosis.

The history of her past illnesses was noncontributory. Repeated skin tuberculin tests were negative.

The family history was negative for pulmonary tuberculosis.

At the age of eighteen the patient had worked for one year as a salesgirl and office receptionist. At nineteen, on March 17, 1941, she began work in the same factory where thy third patient (Case 3) was working at the time. The present patient was placed in the sprae room and worked there steadily for five years and eight months. For the first two years she

worked on filaments and for the next two years as a utility girl, her work including the spraying of cathodes whenever the regular sprayer was absent. During the last twenty months she worked on loading cathodes. She left the factory on October 15, 1946 to resume office work.

The physical examination revealed shortness of breath. The superficial regional lymph nodes were not enlarged and there were no skin lesions. The fingers were slightly clubbed. The heart sounds were normal. Adventitious sounds were present over the axillary and basal portions of the right lung and over scattered areas of the left lung. The blood pressure was 116 mm. of mercury systolic and 86 mm. diastolic. The vital capacity was 1,900 cc. The weight was 121½ pounds, four pounds below normal and twenty pounds less than in October 1946.

The chest roentgenogram (figure 11, June 21, 1948) revealed a diffuse miliary nodulation throughout both lungs with a superimposed, thinly spread network of larger nodules and

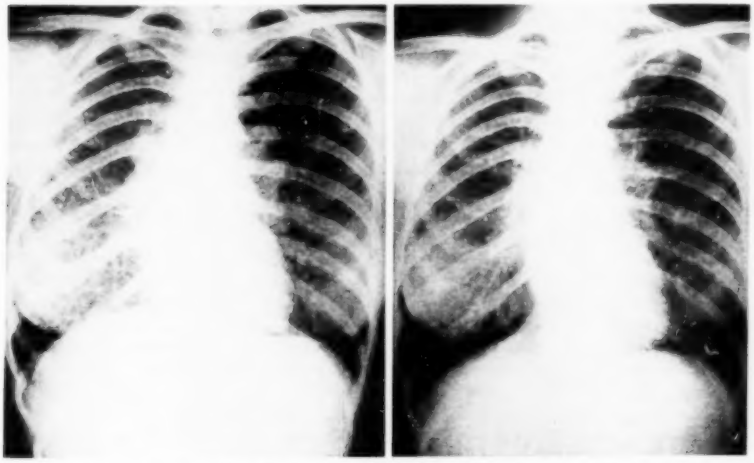


FIG. 11. Case 4. (Left) June 21, 1948. Diffuse miliary nodulation. Beginning reticulonodular infiltration. Heart normal.

FIG. 12. Case 4. (Right) June 18, 1949. Diffuse reticulonodular infiltration, obscuring the original miliary nodulation. Heart normal.

fibrous tissue strands. The root shadows were of increased density. The heart shadow was of a normal configuration. There was a considerable scoliosis with the convexity toward the right.

The granulomatous reaction was still in the early phases of the invasive stage.

Examination on June 18, 1949 revealed progression of the disease. She was still doing office work but complained of increased shortness of breath on slight exertion and after meals. An irritative cough, mucopurulent expectoration, and a sharp pain in the lower portion of the left chest persisted throughout the winter months. She had lost four more pounds in weight. The pulse rate was 72 per minute. The blood pressure was 106 mm. systolic and 88 mm. diastolic. Adventitious sounds were present over major portions of each lung. The heart sounds were normal. The vital capacity was 1,550 cc., a drop of 350 cc. since the examination one year previously.

The chest roentgenogram (figure 12, June 18, 1949) showed considerable connective tissue proliferation through both lung fields, the reticulonodular infiltration overshadowing and

partly obscuring the miliary nodulation. The outline of the left diaphragm became irregular. The heart shadow was normal. The hilar shadows were unchanged.

Thus far, there was no evidence of right ventricular enlargement.

Case 5: The patient, J. D., was a 21-year-old, married, white woman who was first seen on May 4, 1936, when she complained of shortness of breath, cough, profuse expectoration, and weight loss.

The roentgenogram (figure 13, May 4, 1936) revealed a peculiar diffuse haziness overshadowing both lung fields and consisting of fine granules. The hilar shadows were not enlarged and were of a normal density. The heart shadow was of a normal configuration.

Another roentgenogram, taken two weeks later, showed the pulmonary haziness to be increased in density. The sputum was negative for tubercle bacilli.

The patient entered a tuberculosis sanatorium for observation. The hospital records indicate that in 1932, at the age of eighteen, she worked for three months on radio tubes. There was no history of other occupational exposures. Her present illness began in December 1935, three years following the employment in a radio tube factory.

The roentgenogram on admission to the sanatorium (figure 14, June 23, 1936) revealed confluent densities over the lower three-fourths of both lung fields. In some areas scattered larger nodules could be distinguished through the densities. The upper portions of the lungs retained the same haziness which prevailed on the previous films, but the larger vascular markings were surrounded by confluent densities in place of the particulate infiltration. A narrow pneumothorax space separated the upper third of the left lung from the mediastinum and from the dome of the chest. The hilar shadows were obscured. A bulge was present in the region of the pulmonary conus.

She left the sanatorium in September 1936. While there she had repeated febrile attacks, her temperature reaching at one time 102.6° F. Coincident with the febrile attacks were the appearance of confluent densities in the lower portions of the lung fields and around the larger vascular markings. These densities were not stationary and were obviously produced by pulmonary edema. Similar roentgenographic findings were described in the Salem cases (3, 6). Her pulse rate ranged between 108 and 134 per minute. Her weight on discharge was 80 pounds, a loss of 12 pounds since admission. Repeated sputum tests were negative for tubercle bacilli and for fungi. Skin tuberculin tests were also negative.

The roentgenogram on discharge from the sanatorium showed a diffuse granular infiltration in the upper half of each lung field. Some larger nodules were present alongside the vascular markings. Confluent densities, intensified by the breast shadows, were still overshadowing the lower portions of both lungs. The left-sided spontaneous pneumothorax had resorbed. The bulge in the region of the pulmonary conus grew larger. The hilar shadows were still obscured.

She returned to the sanatorium for examination on November 9, 1937. The chest roentgenogram (figure 15, November 9, 1937) showed a diffuse granular infiltration and superimposed scattered clusters of larger nodules throughout both lung fields. The hilar shadows were of a homogeneous density. The right ventricle was markedly enlarged.

She died one month later, on December 13, 1937.

COMMENT

The symptomatology of chronic beryllium granulomatosis is dominated by shortness of breath and by cough. The disease bears no signs of an infectious process and runs a progressive course, uninterrupted by remissions. Because of an insidious onset, the patients seek medical advice with the disease usually far advanced.

A clinical diagnosis is based on a history of exposure to beryllium compounds

and on typical roentgenographic findings. Only in the occasional case can the diagnosis be corroborated during life by recovery of beryllium from the urine.

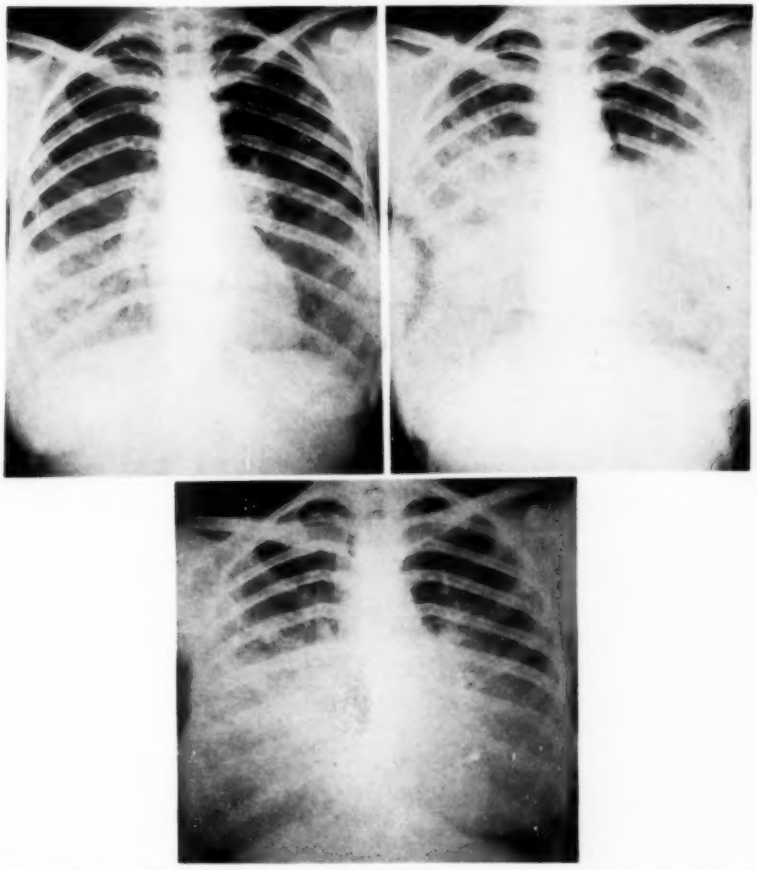


FIG. 13. Case 5. (Upper left) May 4, 1936. Diffuse granular haziness overshadowing lung fields. Heart normal.

FIG. 14. Case 5. (Upper right) June 23, 1936. Confluent densities over lower three-fourths of lung fields. Left-sided spontaneous pneumothorax. Cor pulmonale.

FIG. 15. Case 5. (Bottom) November 9, 1937. Diffuse, predominantly granular infiltration. Marked cor pulmonale.

The post-mortem findings invariably include demonstration of beryllium in the lung tissue.

Evidence of exposure to beryllium: It is certain that beryllium compounds had been used extensively in the radio tube factories at the time the five pa-

tients were working there. The factory workers were not protected against inhalation of finely pulverized phosphors. In the spray room, where the cathodes, grid hooks, and filaments of the tubes were being coated with a mixture of phosphors, even the sprayers were not provided with masks.

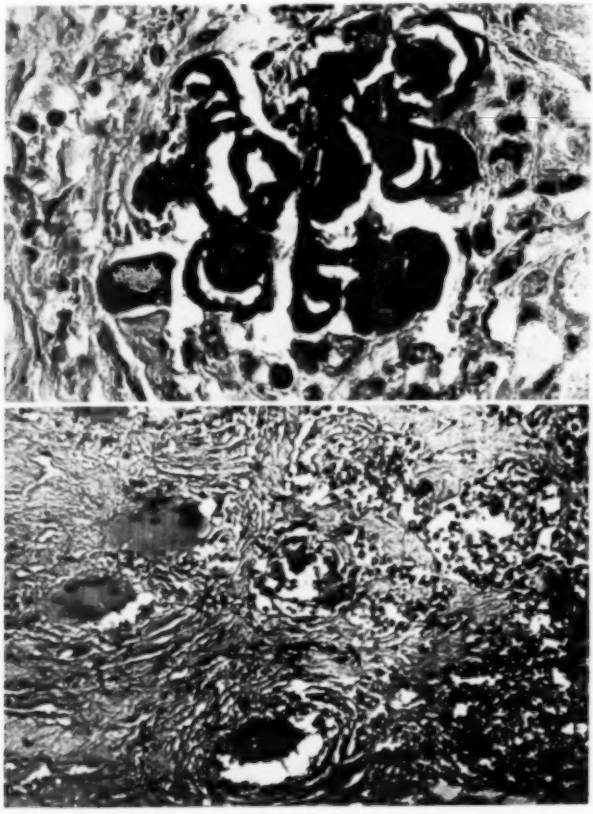


FIG. 16. Case 1. (Top) Inclusion bodies lying free in debris of beryllium granuloma.
FIG. 17. Case 1. (Bottom) Edge of beryllium nodule surrounded by granulation tissue, containing giant cells and acellular tissue infiltrated with lymphocytes.

In the first case, the exposure in radio tube factories was incriminated by the presence of beryllium and other components of the phosphors in her lungs. The added exposure in removing insulation from beryllium copper wires was apparently responsible for the finding of inclusion bodies (figure 16) "of the character and frequency, noted only in two cases of beryllium copper casters, lungs" (2).

The structural features of the granulomas (figure 17) served to distinguish

them from silicosis and from silico-tuberculosis (1, 2). The results of the chemical analysis were also negative for silicosis (low ash value of 4.36 per cent). The inclusion bodies differed from those seen in sarcoidosis (2).

The second patient had been exposed to dust inhalation in three different radio tube factories for a period of more than eight years. She worked for fourteen months in the same factory, where the next two patients developed a similar illness. The nature of the dust could not be specified by the patient, but there was no free silica dust.

The third and fourth patients had been working during a concurrent length of time in the spray room of a radio tube factory. Both had been directly exposed to an atmosphere laden with pulverized phosphors containing beryllium. The exposure of the third patient began one and one-half years earlier and had been more intense because of her work as a full-time sprayer. Consequently, her illness became apparent two and one-half years earlier than that of the fourth patient and has resulted in marked heart damage.

The relationship of exposure to beryllium and the pulmonary granulomatous reaction is obvious in these two cases and has been further substantiated by the occurrence of additional instances of a similar disease among the workers of the same factory.

In the fifth case the details of exposure to dust inhalation in a radio tube factory remain unknown.

Roentgenographic findings: The roentgenographic pattern of the granulomatous reaction was made up of miliary and discrete larger nodules, of composite nodular densities, and connective tissue infiltrates. Diffuse miliary nodulation was present in all cases and probably represented an early phase of invasion. This phase in the three surviving patients had been gradually replaced by a reticulonodular pattern of infiltration, composed of larger nodular densities and connective tissue infiltrates. In the two fatal cases, connective tissue proliferation was scarce and no distinct fibronodular network was observed.

In the first case, large nodules, discrete and conglomerate (figures 18 and 19), were mingled with a diffuse miliary nodulation. Intervening connective tissue was scarce. The pattern of infiltration remained unchanged for a known period of sixteen months.

In the second case, roentgenograms were available for a period of nine years and eight months. The original miliary nodulation has been gradually replaced by a reticulonodular pattern of infiltration.

The third case came under observation with a reticulonodular type of infiltration superimposed on a diffuse miliary nodulation. Within a period of two years the fibronodular network became more diffuse, obscuring most of the minute nodules.

The fourth case was first seen with a diffuse miliary nodulation and a minimal reticulonodular infiltration. Within one year the fibronodular network became more diffuse and overshadowed a large portion of the minute granules.

In the fifth case, a diffuse granular infiltration, described as typical in chronic beryllium granulomatosis (3, 5, 6), prevailed in all roentgenograms for a known

period of eighteen months. There was a constant paucity of fibrous tissue proliferation and of composite nodular formations.

None of the cases developed plaques, or massive conglomerations, as seen in silicosis with the advent of severe symptoms.

Deposition of calcium in the granulomas represents apparently the end phase in their evolution. The presence of calcium deposits in some of the nodules was

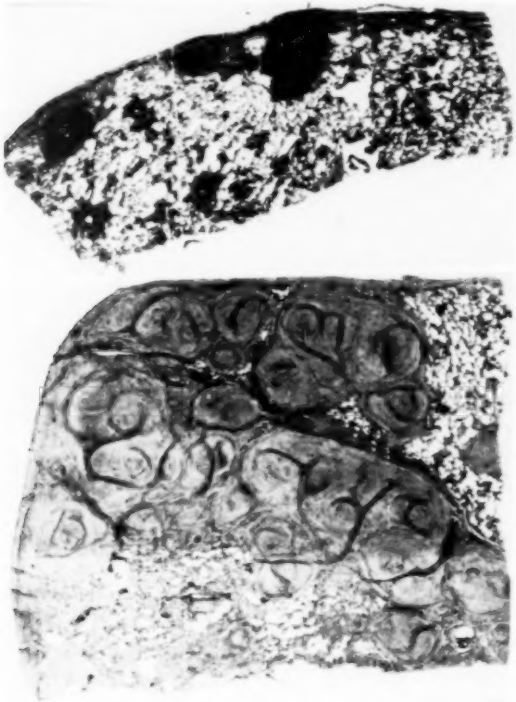


FIG. 18. Case 1. (Top) Discrete beryllium granulomas, 2 to 3 mm. in diameter. Emphysema.

FIG. 19. Case 1. (Bottom) Conglomerate beryllium granulomas, 4 to 8 mm. in diameter. Emphysema.

confirmed by Von Kossa stain in the first case. Widespread calcification of the nodules was obvious in the second case.

Multiple bleb formation was observed in all cases and appeared graphically as rarefied areas surrounded by groups of nodules. A cavity in the upper lobe of the right lung was present in the first case. As stated in the pathological report, "the cavity was either the result of anemic necrosis, or of bleb formation. There is little to indicate that this cavity resulted from necrosis of tissue, incident to bacterial infection" (2).

In the third case, the lower portion of the right lung contained linear areas of atelectasis, with a resulting elevation of the diaphragm and crowding of the nodules on that side.

The hilar shadows were increased in size and density, particularly in the two fatal cases. Bronchial lymph nodes in the first case included units measuring 2 cm. in diameter.

Complications: Spontaneous pneumothorax occurred in both fatal cases. None was observed in the three surviving patients with marked fibrous tissue proliferation. It is possible that the symptoms of a ruptured lung are overlooked in some instances because of pre-existing shortness of breath.

Enlargement of the right ventricle (cor pulmonale) was present in the first, third, and fifth cases. The right-sided pleural effusion in the first case resulted from congestive heart failure. Peritoneal and pericardial effusions were also present.

Continuous mucopurulent expectoration was indicative of bronchiectasis, resulting from distortion of the bronchial tree by the granulomatous process.

Treatment: The dyspnea and cough were aggravated in all cases by cold weather. Thus, it is believed that a change to a mild climate during the winter months would be beneficial to patients with this illness. Profuse mucopurulent expectoration may be relieved in some instances by antibiotic therapy. Early administration of oxygen relieves dyspnea and cough. As this procedure brings relative comfort to the patient, it may prolong life and prevent the occurrence of spontaneous pneumothorax.

SUMMARY

Five cases of chronic pulmonary beryllium granulomatosis are presented, with autopsy findings in one case. The exposure to beryllium compounds occurred in radio tube factories. In the first case, added exposure took place in removing insulation from beryllium copper wires.

The illness appeared to be of lesser severity in cases in which the nodular dissemination was followed by marked connective tissue proliferation.

Calcification of the nodules has been demonstrated in the first and second cases.

SUMARIO

Granulomatosis Pulmonar Difusa en las Jóvenes consecutivamente a la Exposición a los Compuestos del Berilio en la Fabricación de las Ampollas para Radioreceptores

Preséntanse 5 casos de granulomatosis pulmonar crónica por berilio, con los hallazgos autópsicos en uno. La exposición a los compuestos de berilio tuvolugar en las fábricas de ampollas para aparatos de radio. En el primer caso, ocurrió nueva exposición al quitarse el aislamiento de los alambres de cobre-berilio.

La dolencia pareció ser menos grave en los casos en los que la diseminación nodular fué seguida de marcada proliferación del tejido conjuntivo.

En el primero y el segundo casos observóse calcificación de los nódulos.

Acknowledgment

Acknowledgment is made to Dr. Harrison S. Martland for his generous assistance in the studies of the first case. He performed the autopsy himself and was the first to consider the possibility of beryllium poisoning. The case was briefly reported in his paper (4). Four photomicrographs prepared by him are reproduced in this paper.

Histoplasmin concentrate for skin testing was supplied by Eli Lilly and Company.

REFERENCES

(1) Dutra, F. R.: The pneumonitis and granulomatosis peculiar to beryllium workers, Am. J. Path., 1948, *24*, 1137.

(2) Gardner, L. U.: Pathological report presented in part in this paper (December 1944).

(3) Hardy, H. L., and Tabershaw, I. R.: Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds, J. Indust. Hyg. & Toxicol., 1946, *28*, 197.

(4) Martland, H. S., Brodkin, H. A., and Martland, H. S., Jr.: Occupational beryllium poisoning in New Jersey, J. Med. Soc. New Jersey, 1948, *45*, 5.

(5) Pendergrass, E. P., and Robert, A. G.: Some considerations of the roentgen diagnosis of silicosis and conditions that may simulate it, Radiology, 1948, *50*, 725.

(6) Wilson, S. A.: Delayed chemical pneumonitis or diffuse granulomatosis of the lung due to beryllium, Radiology, 1948, *50*, 770.

TUBERCULOSIS AMONG SELECTIVE SERVICE REGISTRANTS[1]

MAPHEUS SMITH, LESTER T. REYNOLDS, AND M. ETHEL HAND

(Received for publication April 12, 1949)

From the Selective Service records of 18,000,000 men examined for military service during World War II has emerged a wealth of data on physical and mental defects and disease conditions surpassing in scope any other such survey ever made in this country. A by-product of the plan for manpower selection for military service, the picture evolved from this survey has far-reaching significance. Of the defects identified, several were active disease conditions. Among these, one of the most important was tuberculosis. Although this disease is no longer the scourge it was a generation ago, it still is sufficiently prevalent for its frequency among all defects and disqualifying defects of examined men to be of great interest.

TOTAL REJECTIONS

Tenth among the leading causes for rejection of physically examined Selective Service registrants still under 38 years of age on August 1, 1945, tuberculosis was responsible for 171,300 or 3.5 per cent of all the registrants who were in Class IV-F and classes with "F" designation on August 1, 1945 who constituted the pool of rejected men.[2] This figure represents only rejections for which tuberculosis was the primary cause. It does not include the thousands who had tuberculosis but were rejected principally for some other disqualifying defect, such as syphilis or illiteracy. The percentage of rejections for tuberculosis among white men (3.9 per cent of total white rejections) was more than twice that for Negroes (1.9 per cent) (table 1).

This race difference in the number of men rejected for tuberculosis is explained to some extent by the fact that only one defect was coded as the principal cause of rejection, and that certain disqualifying defects more common among Negroes than among whites were given precedence in designating the principal cause of rejection. Syphilis, illiteracy, and mental deficiency, more common among Negroes than whites, may be used as examples. When associated with tuberculosis, these defects took precedence as principal defects. As a result, the Negro rejection rates for tuberculosis are not strictly comparable to those for whites. The

[1] Based on Selective Service classification data and sample studies of the results of examination recorded on DSS Forms 200, Reports of Physical Examination, for Selective Service registrants physically examined at local boards in peacetime, and DSS Forms 221, Reports of Physical Examination and Induction, for registrants examined at local boards and induction stations in wartime.

[2] Data in this report include only registrants processed for induction or volunteering for induction through Selective Service local boards. They do not include militarily liable registrants who enlisted directly at armed forces' recruiting stations prior to cessation of such enlistments in December 1942, since no physical examination reports for these registrants were received by the Selective Service System.

exact effect of such a factor on the rejection rates is not known, but data on all recorded defects, reviewed in more detail later in this paper, reveal that Negroes had a lower frequency of tuberculosis per 1,000 examined than was true of whites, although the race difference in all recorded defects was less than in rejection rates.

PROCEDURES OF EXAMINATION AND VARIATIONS IN STANDARDS AFFECTING TUBERCULOSIS REJECTION RATES

Rates of rejection of Selective Service registrants were affected by several important factors. During the total period of procurement there were differences in the average age of the men examined and the proportion of men undergoing re-examination as well as in examination procedures and physical standards.

Standards of acceptability in effect during and immediately preceding World War II were specified by the Army in Mobilization Regulations 1–9.[3] Local board examining physicians as well as Army examiners used these standards in

TABLE 1

*Estimated Number and Per cent of Selective Service Registrants Examined at Ages 18 to 37 and Rejected Because of Tuberculosis and Still under 38 Years of Age on August 1, 1945**

RACE	TOTAL IN REJECTED CLASSES	REJECTED FOR TUBERCULOSIS†	
		Number	Percent
All races	4,828,000	171,300	3.5
White‡	3,909,000	154,000	3.9
Negro	919,000	17,300	1.9

* Includes men in Class IV-F and also those in the occupationally deferred classes, II-A(F), II-B(F), II-C(F). Does not include those with disqualifying tuberculosis for whom other defects were recorded as the principal defects.

† Includes registrants rejected because of obviously disqualifying tuberculosis.

‡ Includes all races other than Negro.

the examination of registrants. During peacetime (November 1940 to the end of 1941) two complete physical examinations were given to many registrants, the first of which was given at the local board and the other at the induction station to registrants forwarded for induction. However, chest roentgenograms were not included at the local board examination unless the physician referred the case to a Medical Advisory Board chest specialist for decision. Beginning in the summer of 1941, chest roentgenograms were made routinely at induction stations. Registrants were designated as acceptable, if examination revealed arrested pulmonary tuberculosis consisting of lesions demonstrated by roentgenographic examination as not exceeding the minimal extent defined in the classification of the National Tuberculosis Association.

[3] *Mobilization Regulations* 1-9, "Physical Standards for Examination during Mobilization," August 1940, March 1942, October 1942, and April 1944, and changes thereto in War Department Circulars and Letters. These standards relating to lungs and chest wall are summarized in "Physical Examinations of Selective Service Registrants," Special Monograph No. 15, Selective Service System, Washington, D. C., 1948, Vol. I, pp. 222-228.

Beginning in January 1942 and continuing through 1943, local board examining physicians rejected, by a screening examination, those registrants obviously disqualified for military service. The arbitrary limits defined by the National Tuberculosis Association as minimal lesions were specified in the Selective Service regulations as the number and size of the apparently healed tuberculous lesions which were acceptable for general military service after induction station examination.

From January 1944 until the end of Selective Service, local board physicians no longer saw each registrant who was called for induction. Instead, registrants who received notices to report to armed forces induction stations for preinduction physical examination might request a local board physical examination, if they believed or knew they had defects which were manifestly disqualifying for military service.

TABLE 2

Per cent of Total Rejections Because of Tuberculosis and Frequency of Tuberculosis per 1,000 Registrants Examined during Selected Time Periods
Continental United States

TIME PERIOD	PER CENT OF TOTAL REJECTIONS			FREQUENCY PER 1,000 EXAMINED		
	All Races	White*	Negro	All Races	White*	Negro
November 1940–September 1941†	2.3	2.3	1.5	9.7	10.3	5.2
April 1942–December 1943‡	3.2	3.5	2.0	19.1	19.9	14.6
February 1944–December 1944‡	3.4	3.7	1.9	35.4	36.9	25.6

* Includes all races other than Negro.
† Figures shown are for local board examinations only.
‡ Local boards and induction stations.

In April 1944 regulations were issued removing the arbitrary limits on the size of the tuberculous lesions, and registrants with calcified residuals of primary tuberculosis were accepted for general service, if the size, number, and character of such lesions did not suggest possible reactivation.

TUBERCULOSIS REJECTION AND FREQUENCY RATES AT THREE DIFFERENT PERIODS

The effects of these varying conditions and standards are best illustrated by comparing the results of physical examination in relation to tuberculosis rejection and frequency rates during several short periods of Selective Service experience. During the peacetime period, 2.3 per cent of all rejections at local board examination were made because of tuberculosis (table 2). This was also the rate for whites, but the Negro rate was 1.5. During this period tuberculosis was recorded for 9.7 registrants in each 1,000 examined, 10.3 for whites and 5.2 for Negroes. This, however, did not include an unknown number of registrants in whom tuberculosis was found at the time of examination by Army medical examiners.

The proportion of rejections for tuberculosis during the second period (April

1942–December 1943) increased to 3.2 per cent and the frequency of tuberculosis to 19.1 per 1,000 examined, almost twice as high as in peacetime. From February 1944 through December 1944, 3.4 per cent of all rejections were for tuberculosis and the frequency of tuberculosis was 35.4 per 1,000 men examined.

The increasing rates for both racial groups during the two wartime periods emphasize the value of the induction station examination with the use of the chest roentgenogram as an aid to diagnosis, in sharp contrast to the peacetime examination at local boards without use of roentgenograms. Also, during the war periods the figures on tuberculosis, particularly those for Negroes, were not reduced as much as during peacetime by the tendency of examining physicians to select diagnoses of venereal disease or of educational deficiency as principal causes for rejection. Educationally deficient registrants were acceptable on a quota basis from August 1942 through June 1943, after which time educational deficiency alone was not a cause for disqualification. And those with uncomplicated gonorrhea or syphilis had become acceptable on a quota basis (October 1942–November 1943) or in as large numbers as treatment facilities permitted (after November 1943). As a result, during the war period tuberculous registrants for whom one or both of these defects had been recorded would probably have the tuberculous condition noted as principal cause for rejection.

The figures shown in table 2 reflect not only differences in examination procedures, but also changes in the composition of the examined groups. During the first, or peacetime, period the men examined were 21 through 35 years of age, mostly single men, and occupational deferments were of prime importance. During 1942 and 1943, the men examined were 18 through 44 years of age (18 to 19 years old beginning on November 13, 1942; 20 years old beginning on February 16, 1942; 21 to 35 years old all during years 1942 and 1943; 36 to 37 years old beginning on February 16, 1942; 38 to 44 years old, February 16, 1942 to December 1942), and even occupational deferments were limited to those employed in essential industries or agriculture. During 1944 men examined were largely 18 through 25 years of age. Thus it can be seen that the second period, 1942 and 1943, was probably more representative of the total male population with respect to tuberculosis than were the other two time periods for which information is available.

TUBERCULOSIS DATA FOR 1940–1944

The remainder of the present paper provides analyses of Selective Service data on tuberculosis with regard to race, age, specific diagnosis of tuberculosis, occupation, and state of residence. In all of these items except the last, the data used begin with November 1940 and end with December 1944. This is the longest period of time for which Selective Service data on tuberculosis are available, and this is the first time data for this combined period have been published. Furthermore, in order to avoid the inevitable duplications caused by re-examination of registrants, a sample of records was selected so as to contain first examinations only, for the periods November 1940–September 1941, April 1942–September 1943, and November 1943–December 1944. For these reasons, the

TABLE 3

Rate of Rejection for Tuberculosis per 100 Registrants Examined, by Race and Age Group
Continental United States

RACE	AGE GROUPS			
	All Ages	18 to 25	26 to 29	30 and over
November 1940–December 1944				
All races	1.6	1.2	1.5	2.4
White*	1.7	1.2	1.6	2.6
Negro	1.1	1.0	1.0	1.4
November 1940–December 1943†				
All races	1.3	0.8	1.1	2.1
White*	1.3	0.8	1.2	2.3
Negro	1.0	0.8	0.9	1.3
January 1944–December 1944‡				
All races	2.7	2.4	2.9	3.4
White*	2.9	2.5	3.1	3.6
Negro	1.6	1.5	1.5	2.0

* Includes all races other than Negro.

† 1940–1943 data based on a 10.4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940–September 1941, inclusive, and on a 6.7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1943–December 1943, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample.

‡ 1944 data based on an approximately 10 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for registrants inducted or rejected during January 1944–December 1944, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports not available for registrants who were found acceptable on preinduction examinations but were not returned for induction.

data presented in the next few pages are considered to give the most reliable facts on tuberculosis among Selective Service registrants during the period of time specified.[4]

[4] The data published by the Selective Service System on tuberculosis have appeared incidentally in four medical statistics bulletins and one special monograph. The rejection rates and frequency rates found in each of these bulletins cover only a part of the whole time period beginning in November 1940 and ending in December 1944 and in most instances do not eliminate other than first examinations. The four bulletins, published by National Headquarters, Selective Service System, are: "Analysis of Reports of Physical Examination," *Medical Statistics Bulletin No. 1*, 1941; "Causes of Rejection and Incidence of Defects," *Medical Statistics Bulletin No. 2*, 1943; "Physical Examinations of Selective Service Registrants During Wartime," *Medical Statistics Bulletin No. 3*, 1944; "Physical Examinations of Selective Service Registrants in the Final Months of the War," *Medical Statistics*

TUBERCULOSIS REJECTIONS BY RACE AND AGE

For the over-all period the rejection rate on first examination for general military service for registrants of all races, aged 18 to 44 years, was 43.9 per cent. The rate of rejection because of tuberculosis was 1.6 per hundred men examined, and increased regularly within each age group (table 3). The Negro rejection rate for tuberculosis was lower than that for white registrants, a differential maintained in each age category.

Table 3 also reveals race and age differentials for the two periods 1940–1943 and 1944 and the same general race difference for each age group and increasing rates with increasing age. The rates for 1944 were higher in all categories than was true of the 1940–1943 rates. The main reasons for this phenomenon were: the more thorough physical examination of men after the speed of mobilization slowed down in 1944 prior to the German counterattack in December 1944, and the fact that educational deficiency and uncomplicated syphilis were no longer the principal cause of rejections, thus causing tuberculosis to be recorded as the principal disqualifying defect in a larger part of the cases examined. Another factor was that the rates after April 1944 did not include records of men aged 26 through 37 years of age who were found acceptable at the time of preinduction examination, but who were never returned for induction because the armed forces reached their planned strength and lowered the upper age of acceptability of men to 25 years.

REJECTIONS BY SPECIFIC DIAGNOSES

Study of the specific diagnoses of tuberculosis discloses that 96.4 per cent of a sample of registrants rejected for tuberculosis during the period November 1940–December 1944 had the pulmonary form and only 3.6 per cent had other kinds of tuberculosis (table 4). These proportions were very consistent for each age group and for both whites and Negroes. Moreover, there was no significant difference between race groups in distribution of diagnoses.

About one-third of pulmonary tuberculosis cases were active for the all ages-all races group, and over 43 per cent were arrested, while almost one-fourth were cases unspecified as to whether active or arrested. The proportion of active cases increased with age, as did the unspecified cases, while the percentage of arrested cases, over half of all in the 18 to 25 year group, decreased rapidly as age increased. These same trends were exhibited for both whites and Negroes, except that among Negroes there was no distinct age trend for unspecified diagnoses of tuberculosis.

Two important differences appear in the specific diagnoses for the period 1940–1943, compared with those for 1944. A total of 95.3 per cent of cases were diagnosed as pulmonary in the 1940–1943 period, compared with 98.3 per cent

---

Bulletin No. 4, 1946. The monograph was "Physical Examination of Selective Service Registrants," *Special Monograph No. 15*, Selective Service System, Washington, D. C., 1948, 3 volumes.

TABLE 4

Per cent Distribution of Tuberculosis Rejections, by Specific Diagnoses, by Age and Race Group
Continental United States

November 1940–December 1944*

CAUSE FOR REJECTION	AGE GROUPS			
	All Ages	18 to 25	26 to 29	30 and Over
All Races				
Total tuberculosis	100.0	100.0	100.0	100.0
Pulmonary tuberculosis	96.4	96.7	96.0	96.4
Active	31.8	24.4	33.0	38.2
Arrested	43.1	54.0	41.0	33.8
Suspected or unspecified	21.5	18.3	22.0	24.4
Other tuberculosis	3.6	3.3	4.0	3.6
White†				
Total tuberculosis	100.0	100.0	100.0	100.0
Pulmonary tuberculosis	96.4	96.7	96.0	96.3
Active	31.5	24.0	32.8	37.8
Arrested	43.6	54.8	41.7	34.2
Suspected or unspecified	21.3	17.9	21.5	24.3
Other tuberculosis	3.6	3.3	4.0	3.7
Negro				
Total tuberculosis	100.0	100.0	100.0	100.0
Pulmonary tuberculosis	96.7	96.8	95.6	97.0
Active	34.5	27.7	34.5	41.8
Arrested	38.6	47.6	34.9	30.4
Suspected or unspecified	23.6	21.5	26.2	24.8
Other tuberculosis	3.3	3.2	4.4	3.0

* 1940–1943 data based on a 10.4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940–September 1941, inclusive, and on a 6.7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1942–December 1943, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample. 1944 data based on an approximate 10 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for registrants inducted or rejected during January 1944–December 1944, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports not available for registrants who were found acceptable on preinduction examinations but were not returned for induction.

† Includes all races other than Negro.

in 1944.[5] The same high consistency in the proportion of pulmonary diagnoses in each age group occurred during both periods of time and for each race.

The most outstanding difference between the two periods of time was in the decline in the proportion of unspecified pulmonary cases in 1944, compared with the 1940–1943 period. From one-third of all cases in the 1940–1943 period with unspecified pulmonary diagnoses, the proportion fell to 3.4 per cent in 1944. Almost all of the proportionate increase in specified cases was in the arrested category (from 33.2 per cent of all cases to 58.6 per cent). The decrease in the percentage of unspecified pulmonary tuberculosis in 1944, compared to 1940–1943, was probably a result of the fact that during 1944 virtually all registrants were examined at armed forces induction stations and the examiners were better equipped than were local board examining physicians to determine whether the disease process was active or arrested.

The same upward trends with age for active pulmonary diagnoses and downward trends for arrested cases were found for each of the two periods of examination, but there was no trend with age in either period for the unspecified cases. These facts also apply to each race group in each of the two periods.

FREQUENCY OF TUBERCULOSIS

The employment of modern improved methods of diagnosis in the vigorous campaign waged against tuberculosis within the past several decades has disclosed many latent cases. Hence it is impossible to draw a valid comparison between the frequency of tuberculosis during the two world wars. Tuberculosis was recorded for 4.9 out of every 1,000 of the first million men examined in World War I and for 19.8 per 1,000 Selective Service registrants examined, November 1940–December 1944. In view of the fact that the national death rate from tuberculosis has declined sharply in the period between the two wars, the increased frequency of tuberculosis in Selective Service registrants appears to reflect the improvement in methods of detection.

Timely discovery of the disease during World War II examinations not only kept out of service men whose military contributions would have been ineffectual, but also put many tuberculosis cases under remediable treatment leading to potential recovery. The effect of improved diagnosis shows up in disability discharges also. Thus, whereas tuberculosis, as the largest single cause, accounted for 10.9 per cent of all disability discharges during World War I, only about 2.6 per cent of the veterans of World War II, who were receiving disability awards in September 1944, had tuberculosis as their major disability.

Information on the frequency of disease is invaluable in supporting the establishment of any plan for control and eventual elimination of the disease. Keener insight into the problem of tuberculosis is afforded by data on the number of cases found among each 1,000 men examined, regardless of acceptance or rejection for induction. Table 5 presents such data on the frequency of occurrence of

[5] In order to conserve space, tables showing the differences between the 1940–1943 and 1944 data have been omitted. These data are available to interested readers at National Headquarters, Selective Service System.

TABLE 5

Frequency of Specific Diagnoses of Tuberculosis per 1,000 Registrants Examined, by Race and Age Group
Continental United States
November 1940–December 1944*

CAUSE FOR REJECTION	AGE GROUP			
	All Ages	18 to 25	26 to 29	30 and Over
All Races				
Total tuberculosis	20.1	14.7	19.2	30.5
Pulmonary tuberculosis	19.4	14.2	18.4	29.5
Active	6.2	3.4	6.1	11.3
Arrested	8.9	8.0	8.0	10.8
Suspected or unspecified	4.3	2.8	4.3	7.4
Other tuberculosis	0.7	0.5	0.8	1.0
White†				
Total tuberculosis	20.8	15.0	19.8	32.5
Pulmonary tuberculosis	20.1	14.5	19.0	31.4
Active	6.3	3.4	6.2	11.9
Arrested	9.3	8.3	8.4	11.6
Suspected or unspecified	4.5	2.7	4.4	7.9
Other tuberculosis	0.7	0.5	0.8	1.1
Negro				
Total tuberculosis	15.5	12.9	15.2	19.7
Pulmonary tuberculosis	15.0	12.6	14.5	19.2
Active	5.2	3.6	5.2	7.9
Arrested	6.3	6.3	5.9	6.6
Suspected or unspecified	3.5	2.7	3.4	4.7
Other tuberculosis	0.5	0.3	0.7	0.5

* 1940–1943 data based on a 10.4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940–September 1941, inclusive, and on a 6.7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1942–December 1943, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample. 1944 data based on an approximate 10 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for registrants inducted or rejected during January 1944–December 1944, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports not available for registrants who were found acceptable on preinduction examinations but were not returned for induction.

† Includes all races other than Negro.

tuberculosis at time of first examination by specific diagnoses among men examined at 18 to 44 years of age during November 1940–December 1944.

Table 5 shows that approximately 20 out of every 1,000 men examined were

found to have tuberculosis in some form, 6 of whom had active pulmonary cases, 9 arrested pulmonary cases, and 4 unspecified pulmonary cases, while less than one per 1,000 had tuberculosis of parts of the body other than the lungs. All of these rates rose with age.

Negroes had lower occurrence rates of all sorts than was true for whites, except for active cases among men 18 to 25 years of age, where the difference was small. Another white-Negro difference was that there was no clear relationship between age and the frequency of arrested cases of pulmonary tuberculosis among Negroes, while there was an increase in rates with increasing age among whites. And a third was the failure of Negroes to show a consistent increase with age in the frequency of forms of tuberculosis other than pulmonary.

When the November 1940–December 1943 experience is separated from that of 1944, a few important differences in frequency rates are noticed. The rates for the earlier period were less than half as large as for 1944, but at the same time there was a great reduction in the proportion of cases with unspecified pulmonary tuberculosis.[6] The proportionate increase in arrested pulmonary tuberculosis discovered was particularly pronounced, doubtless because of improved techniques and the universal use of roentgenography in diagnosis during all of the 1944 period.[7] The only other noteworthy difference was that in 1944 there was no consistent increase in the frequency of arrested pulmonary tuberculosis with age for the Negro group, but the white and all race groups showed a regular increase with increasing age in this form of diagnosis.

OCCUPATIONAL DIFFERENTIALS IN OCCURRENCE OF TUBERCULOSIS

Analysis of physical examination data by occupation reveals considerable differences in frequency rates. The unemployed and those who did not report occupation had the highest over-all frequency rates (table 6). Also over the average for all groups were professional workers, proprietors, service workers, and craftsmen, while laborers and farmers were below average.

The rates increased in size in most occupational groups with increasing age, the exceptions being domestic service workers and farm laborers and foremen.

There was great variability in frequency rates by occupation for the two major racial groups. Although Negroes had a smaller rate than whites for all occupations, they surpassed whites in rates for clerical and sales workers, and protective service workers.

Analysis by period of time reveals that the high rate of tuberculosis frequency for most of the groups mentioned above was characteristic of both the 1940–1943 and 1944 periods of examination.[8] The age differentials by race and occupation also seem to have been general in both periods of time.

[6] In order to conserve space, tables showing the differences between the 1940–1943 and 1944 data have been omitted. These data are available to interested readers at National Headquarters, Selective Service System.

[7] In this connection should be cited the special effort made by personnel of the Office of the Surgeon General of the Army to diffuse throughout all examining stations comparable use of diagnostic techniques.

[8] In order to conserve space, tables showing the differences between the 1940–1943 and 1944 data have been omitted. These data are available to interested readers at National Headquarters, Selective Service System.

TABLE 6

Frequency of Tuberculosis Per 1,000 Registrants Examined in Each Major Occupational Group, by Race and Age Group
Continental United States

November 1940–December 1944*

OCCUPATIONAL GROUP	RATE PER 1,000 EXAMINED											
	All Races				White†				Negro			
	All Ages	18 to 25	26 to 29	30 and over	All Ages	18 to 25	26 to 29	30 and over	All Ages	18 to 25	26 to 29	30 and over
All occupations	20.1	14.7	19.2	30.6	20.8	15.0	19.8	32.5	15.5	12.9	15.2	19.7
Professional and semiprofessional	21.9	13.8	18.0	33.6	22.4	14.0	18.3	34.7	11.3	7.3	12.2	13.9
Proprietors, managers, and officials	24.2	9.3	16.6	33.1	24.5	9.4	16.8	33.5	9.6	5.3	6.3	11.8
Clerical and sales	19.6	11.7	17.9	33.9	19.5	11.4	17.7	33.9	25.1	19.2	26.9	35.3
Domestic service workers	21.0	16.8	9.6	27.0	36.6	33.1	26.0	39.9	15.6	12.4	5.9	21.2
Protective service workers	25.8	15.1	25.5	30.6	25.6	14.2	25.0	30.8	31.4	37.0	42.6	25.2
Other service workers	24.0	15.7	21.9	33.0	27.3	15.5	23.5	38.9	18.6	16.0	19.3	21.5
Craftsmen, foremen, and kindred workers	21.7	15.5	20.0	29.9	21.8	15.4	19.9	30.5	19.4	16.4	21.7	21.2
Operatives and kindred workers	18.3	13.5	18.5	29.0	18.5	13.3	18.7	30.2	17.0	14.8	16.8	20.0
Farmers and farm managers	16.1	12.8	13.5	21.9	17.3	14.0	14.0	23.1	9.9	6.9	11.2	14.4
Farm laborers and foremen	16.0	15.4	13.4	19.9	17.4	16.7	13.5	22.5	11.3	10.6	13.3	12.1
Laborers other than farm	15.0	12.0	13.9	21.1	16.2	12.4	16.0	24.3	12.5	11.0	9.8	15.8
Students	15.5	15.2	21.4	26.1	15.6	15.3	21.6	25.9	13.6	13.3	17.9	29.4
Nonclassifiable	9.9	6.5	9.6	17.5	10.2	6.5	10.6	18.0	7.5	6.4	—	14.2
Unemployed and emergency workers	32.4	22.6	33.3	51.2	34.9	24.1	36.5	55.6	21.2	15.0	19.6	32.8
Unknown	36.7	30.4	35.0	48.6	38.9	32.7	36.1	51.6	26.8	19.9	29.8	35.7

* 1940–1943 data based on a 10.4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940–September 1941, inclusive, and on a 6.7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1942–December 1943, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample. 1944 data based on an approximate 10 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for registrants inducted or rejected during January 1944–December 1944, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports not available for registrants who were found acceptable on preinduction examinations but were not returned for induction.

† Includes all races other than Negro.

TABLE 7

Frequency of Tuberculosis Defect Per 1,000 Selective Service Registrants Physically Examined by State and Race

November 1940–December 1943*

STATE	TOTAL	WHITE†	NEGRO
United States, Continental	15.5	15.9	12.7
Alabama	9.5	7.4	12.5
Arizona	49.3		
Arkansas	18.0	19.1	15.6
California	22.6	22.3	29.0
Colorado	24.5		
Connecticut	10.9	10.7	17.0
Delaware	16.5	17.3	13.5
District of Columbia	18.4	19.6	16.3
Florida	9.8	11.8	7.4
Georgia	7.1	5.1	10.6
Idaho	6.7		
Illinois	21.1	21.0	22.6
Indiana	20.9	20.7	25.6
Iowa	9.5		
Kansas	7.0	6.9	8.4
Kentucky	25.6	25.2	29.5
Louisiana	10.4	11.0	9.6
Maine	9.9		
Maryland	18.4	19.6	14.6
Massachusetts	14.0	13.9	20.8
Michigan	12.7	12.3	19.3
Minnesota	9.8		
Mississippi	6.6	8.3	5.3
Missouri	18.0	17.8	19.7
Montana	9.9		
Nebraska	13.1		
Nevada	13.6		
New Hampshire	9.4		
New Jersey	11.4	11.5	10.4
New Mexico	43.5		
New York City	17.5	17.3	20.1
New York (except N.Y.C.)	15.6	15.6	18.1
North Carolina	7.1	8.2	5.0
North Dakota	9.1		
Ohio	19.7	19.4	24.3
Oklahoma	9.4	9.4	9.6

* 1940–1943 data based on a 10.4 per cent sample of DSS Forms 200 (Reports of Physical Examination) for the period November 1940–September 1941, inclusive, and on a 6.7 per cent sample of DSS Forms 221 (Reports of Physical Examination and Induction) for the period April 1942–December 1943, inclusive; they do not include reports of second and subsequent examinations of registrants, to avoid possible duplication of data. Reports for registrants examined and later deferred for other than physical or mental reasons are excluded from the sample.

† Includes all races other than Negro. Separate data for whites and Negroes not shown for the states having less than 0.3 per cent of the total U. S. Negro registrants in the first, second, third, fifth and sixth registrations.

TABLE 7—*Continued*

STATE	TOTAL	WHITE†	NEGRO
Oregon	12.1		
Pennsylvania	13.8	13.8	14.0
Rhode Island	21.2		
South Carolina	5.7	6.7	4.5
South Dakota	10.2		
Tennessee	18.0	18.6	15.9
Texas	15.4	16.6	11.3
Utah	2.9		
Vermont	11.7		
Virginia	17.9	19.9	13.7
Washington	14.8		
West Virginia	26.1	26.0	27.1
Wisconsin	14.2		
Wyoming	4.9		

VARIATIONS BY STATE OF RESIDENCE

According to the records of men given physical examination during the period November 1940–December 1943, the frequency of tuberculosis was lowest in Utah (only 2.9 per 1,000 men (table 7)). In general, greater freedom from tuberculosis seems to be found in western and northwestern states and in some of the southern states. Wyoming, South Carolina, Mississippi, Idaho, Kansas, Georgia, North Carolina, and North Dakota showed a low rate for tuberculosis. The frequency rate was higher than the national average of 15.5 in Arizona, New Mexico, West Virginia, Kentucky, Rhode Island, Illinois, Indiana, Ohio, District of Columbia, Maryland, Missouri, Arkansas, Virginia, New York City, and Delaware. Migrations of many tuberculous patients to such states as Colorado, California, New Mexico, and Arizona, and many from other states undoubtedly affect the rates to some extent. The amount of such an effect could not be determined, however, without information being available on place of residence at time of the appearance of the disease and date of change of residence to state of registration.

In several states the frequency of tuberculosis per 1,000 registrants examined was higher for Negroes than for whites. Most of such states were in the North and West, where the crowding of low-income Negro groups in city slums may have been a factor in the larger rates. On the other hand, several of the southern states revealed very low tuberculosis rates for Negroes, largely a result of their rural occupation and place of residence. Exceptions to this rule were Alabama and Arkansas where Negro rates for tuberculosis were at or above the national average. The explanation of these and other state variations is not readily apparent from available information, but it is obvious that a number of factors are needed to explain the state and Negro-white differentials.

SUMMARY

The outstanding facts regarding tuberculosis in the health picture developed from Selective Service records may be summarized as follows:

1. Tuberculosis was tenth in importance as cause for rejection and responsible for 171,300 or 3.5 per cent of all rejections of examined men aged 18 to 37 as of August 1, 1945.

2. Rejection data were affected, to some extent, by ages of men examined, changes in physical examination procedures, and changes in physical standards. A potent factor affecting increase, both in rejections and in frequency of tuberculosis discovered during the war years, was the use of the chest roentgenogram.

3. Specific diagnoses of tuberculosis indicate that 96.4 per cent of tuberculosis rejections were for pulmonary tuberculosis during 1940–1944, and that about one-third were for active pulmonary tuberculosis.

4. The marked increase in recorded cases of tuberculosis during World War II, as compared with World War I, is indicative of progress in methods of diagnosis, particularly the use of the chest roentgenogram.

5. Out of every 1,000 men examined through Selective Service during 1940–1944, 20.1 were found to have some form of tuberculosis. Negroes, throughout Selective Service experience, showed lower rates for tuberculosis than did white men.

6. The rejection rate for tuberculosis and the frequency of the disease per 1,000 men examined tended to increase as age increased. This was true for both Negroes and whites.

7. Rejection and frequency rates were higher in 1944 than in 1940–1943 because of statistical factors affecting the computation of the rates.

8. Unemployed men, proprietors, and protective service workers showed the highest frequency of tuberculosis per 1,000, and laborers and students the lowest. Those engaged in out-of-doors work generally manifested less susceptibility to the disease than white collar workers. The rates were generally lower for Negroes than whites in most occupations, and increased with age.

9. State comparisons show that the frequency of tuberculosis was lowest in Utah (2.9 per 1,000 examined) and, except for New Mexico and Arizona, highest in West Virginia and Kentucky, with rates per thousand of 26.1 and 25.6, respectively. Nineteen states had frequency rates above the national average of 15.5 per 1,000 examined during the period November 1940–December 1943.

SUMARIO

Tuberculosis entre los Inscritos para el Servicio Militar Selectivo

Los datos sobresalientes con respecto a tuberculosis que aparecen en el cuadro sanitario formado por los protocolos del Servicio Militar Selectivo, pueden sumarizarse en esta forma:

1. La tuberculosis ocupa el décimo puesto en importancia como causa de rechazos, habiendo motivado 171,300, o sea 3.5 por ciento, de todos los rechazos de sujetos examinados de 18 a 37 años, hasta el 1° de agosto de 1945.

2. Los datos de rechazo fueron afectados, hasta cierto punto, por la edad de los sujetos examinados, las modificaciones de los procedimientos de examen físico y las modificaciones de las pautas físicas. Un factor potente que afectó el

aumento, tanto en rechazos como en la frecuencia de tuberculosis, fué el empleo de la radiografía torácica.

3. Los diagnósticos específicos de tuberculosis indican que 96.4 por ciento de los rechazos por tuberculosis fueron por tuberculosis pulmonar durante 1940–1944, y aproximadamente la tercera parte por tuberculosis pulmonar activa.

4. El decidido aumento en los casos de tuberculosis inscritos durante la II Guerra Mundial, comparada con la I, refleja el adelanto realizado en los métodos de diagnóstico, y en particular el empleo de las radiografías torácicas.

5. De cada 1,000 individuos examinados por el Servicio Selectivo durante 1940–1944, 20.1 mostraron tener alguna forma de tuberculosis. Los negros, en todas las observaciones del Servicio, revelaron coeficientes de tuberculosis más bajos que los blancos.

6. El coeficiente de rechazos por tuberculosis y la frecuencia de la enfermedad por 1,000 sujetos examinados tendió a aumentar a medida que avanzaba la edad, lo cual rezó con negros y blancos.

7. Debido a factores estadísticos que afectaron la computación de las tasas, los coeficientes de rechazos y de frecuencia fueron más altos en 1944 que en 1940–1943.

8. Los desocupados, los propietarios y los empleados en servicios de resguardo revelaron la mayor incidencia de tuberculosis por 1,000 y los trabajadores y los estudiantes la menor. Los dedicados a trabajos al aire libre manifestaron en general menos susceptibilidad a la enfermedad que los empleados en oficinas, tiendas, etc. Las tasas fueron generalmente más bajas para los negros en la mayoría de los oficios y avanzaron con la edad.

9. Comparaciones por estados revelan que la incidencia de tuberculosis alcanzó el mínimo en Utah (2.9 por 1,000 examinados), y aparte de Nuevo México y Arizona, el máximo en la Virginia Occidental y Kentucky, con coeficientes de 26.1 y 25.6, respectivamente, por 1,000. Diecinueve estados mostraron coeficientes superiores al promedio nacional de 15.5 por 1,000 examinados durante el período de noviembre, 1940–diciembre, 1943.

Case Reports

PULMONARY ALVEOLAR ADENOMATOSIS[1, 2]

SIDNEY J. SHIPMAN, H. BRODIE STEPHENS, AND FREDERICK M. BINKLEY

(Received for publication May 5, 1949)

INTRODUCTION

In March 1945 David A. Wood and Philip H. Pierson (1) reported the first case of pulmonary alveolar adenomatosis in which the diagnosis had been made before death. In this patient the diagnosis was established by a lobectomy which was done by Dr. Emile Holman six months prior to death. This case was a unique contribution to the literature because the diagnosis was not only made ante mortem but the possible virus etiology of the disease was considered and studies were made in the attempt to prove the etiological factor. Largely because of the interest aroused by this patient and the fact that one of us was able to follow the case with Pierson at the time of his study, it was possible to arrive at diagnosis prior to operation in the case here reported.

Pulmonary alveolar adenomatosis is said to be a rare disease in man, although probably sixteen authenticated cases have now been reported. Among the cases so far reported are those of Lohlein (2), Sims (3), Obendorfer (4), Helly (5), Bonne (6), Richardson (7), Briese (8), Bell (9), Taft and Nickerson (10), three additional cases reported by Paul and Ritchie (11), and three by Drymalski, Thompson, and Sweany (12). Two of the human cases reported were associated with extension to the peribronchial lymph nodes. The etiology of the human disease is still in doubt and the pathogenesis is far from clear. The disease is certainly rare but bears a remarkable resemblance to benign pulmonary adenomatosis which has been reported as occurring epizootically in the sheep of South Africa, Iceland, England, and the United States, especially in certain areas of Montana. Characteristically the disease appears when sheep are being driven from place to place; hence the South African name "Jaagsiekte" or "driving disease." In Montana it has been called progressive pneumonia. The disease was first discovered in South Africa in 1893. It appeared for the first time in Iceland in 1934 and then spread so rapidly that it aroused widespread interest. Apparently it can be introduced into uninfected flocks by sick animals and it is said that animals which merely occupy the quarters previously occupied by infected animals may themselves become ill. In sheep, both sexes and all ages appear to be susceptible. There is only one instance in the literature in which mitoses have been observed in "Jaagsiekte."

For the most part the disease is very insidious and runs a chronic course. Several weeks may pass before it is suspected. Early disease is, therefore, customarily missed, especially if the flock remains at rest. In the later stages the breathing is said to cause a characteristic sound which resembles "slowly boiling porridge" due to the moist rales which may be audible at some distance. Ultimately, secretion pours from the mouth

[1] From the Departments of Medicine and Surgery, University of California Medical School, San Francisco.

[2] Presented before the Medical Section, as part of the symposium on *Nontuberculous Diseases*, at the 45th annual meeting of the National Tuberculosis Association, Detroit, Michigan, May 5, 1949.

and nostrils and the sheep stand with lowered heads to free themselves of secretion. The incubation period is said by Dungal to vary from six to eight months and Dungal was impressed by a possible hereditary factor. Attempts to demonstrate the etiological agent, either virus or bacterial, were uniformly negative. Intrapulmonary inoculation has been said to be a successful method for transfer of the disease in one of three attempts with farm animals. However, housing sheep together appears to lead to transmission without difficulty. The histological factor consists of characteristic epithelial proliferation with formation of papillary intra-alveolar masses which are not invasive but preserve the stromal outlines of the alveoli.

CASE REPORT

The patient is a white, married female, 51 years of age. Her family history, marital history, and past history until eight or nine years ago seemed to be entirely noncontributory except that in 1939 or 1940 her neighbors had a small flock of sheep which fell ill with an acute type of pulmonary infection from which many of the sheep died. The patient's contact was casual, involving an interest in the misfortune of her neighbors but not to the extent of any care of the sick animals. At about this time, however, or shortly thereafter, she noticed the appearance of a dry, hacking cough which was irritative and nonproductive. She believes that in 1941 or 1942 she began to raise small amounts of clear, mucoid, frothy sputum and that at the same time her cough became rather more prominent. She consulted a physician because of her pulmonary symptoms at that time. Her physical examination was essentially negative but roentgenographic examination was said to show some abnormal findings in the region of the right lower lobe, although the film was lost or misplaced and could not be obtained for comparison with subsequent roentgenograms. The diagnosis at this time was bronchiectasis involving the right lower lobe. Meanwhile, however, her symptoms gradually became worse. The sputum increased, although it remained mucoid and frothy. In 1944 her symptoms became more severe and a film of this date was also said to reveal a pathological process in the right lower lobe and bronchograms were said to show bronchiectasis. In 1945 the cough became still more marked and the right lower lobe lesion again appeared in the roentgenogram. This film, dated June 6, 1945, revealed an area of increased density roughly triangular in shape, lying just above the diaphragm and posterior to the interlobar septum between the right middle and lower lobes (figure 1). A bronchoscopy was essentially negative. The sputum, which up to this time had been glairy, white mucus, became thick, yellow, and foul-smelling and the patient described a troublesome musty odor. She was also troubled by vague right lower chest pain which was never pleuritic in character.

A film taken in July 1946 revealed slight enlargement of the shadow previously described in the film a year earlier. A year later, however, in July 1947, the anteroposterior film (figure 2) revealed a shadow which looked more extensive but nevertheless similar to the preceding ones, although the latter film showed that the process behind the interlobar septum had apparently cleared. The area of density now occupied a triangular area lying against the posterior chest wall, the area above the diaphragm being free. A film taken on December 15, 1947 did not differ from that taken in July of the same year.

Examination of the blood showed the hemoglobin to be 101 per cent, red blood cells 4,970,000 per cu. mm., white blood cells 14,150 per cu. mm., with a differential count of polymorphonuclears 86 per cent, eosinophils 1 per cent, basophils 0, lymphocytes 9 per cent, and monocytes 4 per cent.

Because of the previous rather casual exposure to sick sheep, the long insidious illness to which no other etiology could be ascribed, and the striking resemblance of the patient to the Wood and Pierson case reported in 1945, a diagnosis of pulmonary alveolar adenomatosis was made. Since no therapy had heretofore proved effective in this disease and since it appeared to be limited to the right lower lobe, right lower lobe lobectomy was agreed upon. Accordingly, on May 4, 1948 the right lower lobe was removed. It was found

to be quite free, firm throughout, salmon-pink in color, with a peculiar, smooth, solidified surface. The pathological report follows:

Material from Right Lower Lobe Lobectomy

Gross description: The specimen consisted of a right lower lung lobe, weight 470 Gm., with a smooth pleural surface. The lung parenchyma was very soft and mushy with a salmon-pink color. In many areas it had a pearly-white, granular appearance. Often the alveoli appeared to be distended with this mucoid material. A small portion of the most

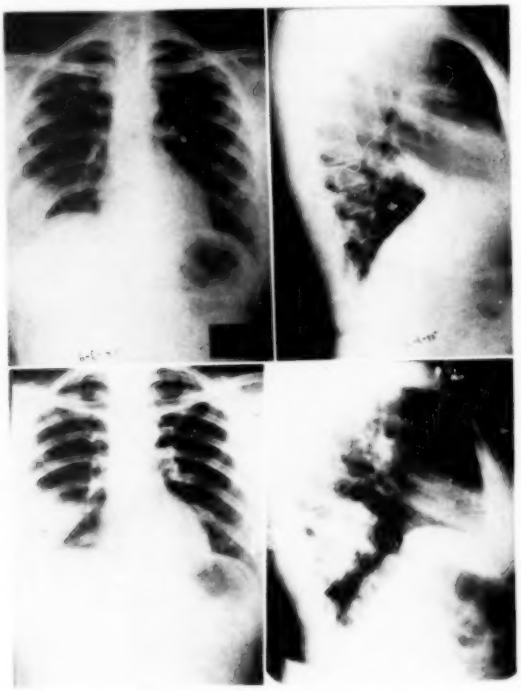


FIG. 1. (Top) Triangular density right lower lobe, posterior to interlobar septum, June 6, 1945.

FIG. 2. (Bottom) July 17, 1947. Original area lying posterior to interlobar septum has cleared. Density now occupies posterior half of right lower lobe.

superior portion showed rare, normal, congested lung tissue. The bronchi were free from tumor and a few small, pigmented hilar lymph nodes were present.

Microscopic: The alveoli showed varying degrees of metaplasia and replacement by a simple columnar type of mucus-secreting cell. The cells were somewhat hypertrophic but well differentiated and mitoses were uncommon. Varying degrees of differentiation were present and occasionally well-formed goblet cells were found. The cells frequently had a polypoid appearance. The alveoli were often distended by these cells. The uninvolved alveoli often were distended with mucus and mucoid-containing macrophages. Occasional groups of chronic inflammatory cells were noted with early fibrosis of the alveolar walls.

The bronchioles were somewhat dilated and often contained mucus. At the margin of the more normal lung noted grossly, the pulmonary parenchyma was compressed and the nearby alveoli were distended with many large reticulo-endothelial cells with finely granular cytoplasm. There were large numbers of eosinophils and considerable intra-alveolar bleeding. The bronchioles and bronchi in this region also were compressed and the smaller blood vessels showed perivascular cuffing with chronic inflammatory cells and eosinophils. The pleura showed an increased number of chronic inflammatory cells. The hilar lymph nodes showed only moderate anthracosis with a slight increase in the number of eosinophils.

The diagnosis was pulmonary adenomatosis.

Following lobectomy the patient made an uneventful recovery. She apparently remained well until February 1949, when a slight discomfort appeared in the right posterior chest and she noticed a recurrence of the glairy mucoid sputum which had previously characterized her disease. A chest film revealed several areas of density in the lower part of the remaining lung. In March 1949 she returned for examination and sputum samples were taken by Dr. Henry Brainerd of the University of California staff for virus studies which are now being carried out. Following the collection of these sputum specimens the patient was given a ten-day course of aureomycin in one-half gram doses every six hours without apparent clinical effect. Fine crepitant rales were present over the lower right chest following the completion of the aureomycin therapy and the shadows on the roentgenogram showed no definite change.[3]

DISCUSSION

While this disease is rare, the writers are of the opinion that it may be somewhat more common than heretofore believed, and it is, therefore, thought worth while to report this patient as one in whom the diagnosis was seriously considered prior to operation. If the disease is of true virus etiology, it is interesting to speculate upon the possible effect of some of the new antibiotics. It is quite possible that opportunities may arise for their trial in the future since the disease is not always localized to one area of the lung but may appear simultaneously in different lobes.

The case for virus etiology is still presumptive. Certainly there is a definite similarity between the morphological appearance of human cases and bovine disease. There is a strong case for the virus etiology of the latter since the transmission from animal to animal appears to be well recognized. So far, however, there is no known recorded instance in which transmission has occurred from man to man.

Is there any relationship between this disease and so-called primary alveolar cell carcinoma of the lung? So far this question remains unanswered. Certainly there are many points of similarity, as will be noted from the microphotograph (figure 3). Nevertheless, the paucity of the mitotic figures and the absence of stromal invasion in our case are more characteristic of pulmonary alveolar adenomatosis. Apparently the hyperplasia of columnar epithelium is primary and stromal changes secondary. An excellent review of the disease as it occurs in Icelandic sheep may be found in Wood and Pierson's article and is, therefore, not repeated here. In the same article appears an excellent discussion of the case for and against virus etiology.

Drymalski, Thompson, and Sweany state that there are no signs or symptoms pathognomonic of pulmonary adenomatosis. Radiologically they say the condition simulates

[3] Shortly after operation sputum from this patient was submitted to Dr. Henry Brainerd of the University of California for virus studies. It was not possible to isolate a virus from the submitted material. Treatment with two standard courses of aureomycin produced no change in the patient's condition. Treatment with 1 Gm. of streptomycin daily for 60 days produced no objective change. The patient is still under observation.

tuberculosis, carcinoma, or pneumonia. In our own case, however, we believed that there were certain features which pointed to the diagnosis. The insidious onset with the long, rather benign course, which was not characteristic of any other chronic pulmonary infection, was suggestive. The fact that the disease appeared to involve the anterior part of the right lower lobe and then shifted to the posterior part of the right lower lobe appeared to be unlike true neoplasm. Nevertheless, the fact that the shadows on the chest roentgenogram never diminished in size, as in atelectasis, seemed to exclude bronchial obstruction. No etiological agent could be recovered from the sputum.

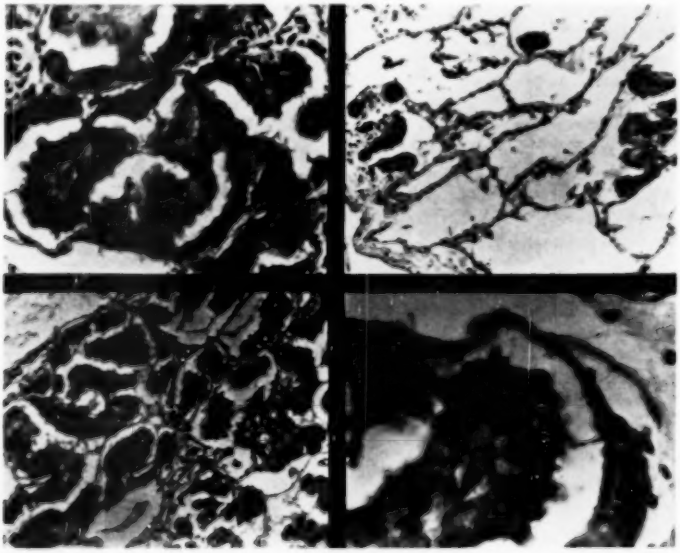


FIG. 3. Alveoli show varying degrees of metaplasia and replacement by a simple type of mucus-secreting cell.

SUMMARY

1. A case of histologically benign pulmonary adenomatosis occurring in the right lower lobe of a 51-year-old, white, married female has been reported.

2. This woman had a definite, though rather casual, exposure to sick sheep shortly before her symptoms began.

3. This is the third recorded human case in which the disease has been diagnosed prior to death and the first case to our knowledge in which the correct diagnosis of the disease has been considered prior to operation.

4. In this case the disease appeared to be limited to the right lower lobe at operation.

5. Symptoms appeared approximately seven years before operation.

6. The onset was insidious, characterized by a dry cough gradually becoming productive, with the late development of dull pain over the involved area.

7. The roentgenographic findings were not characteristic of any other disease. The lesion was not one which produced atelectasis but the involved area remained essentially normal in size unlike most other inflammatory processes.

8. Lobectomy has not produced a cure in that there appears to be a spread of the disease into the remaining lung on the operated side seven months following operation.

SUMARIO

Adenomatosis Alveolopulmonar

1. El caso comunicado es de adenomatosis pulmonar histológicamente benigna en el lóbulo inferior derecho de una mujer blanca, casada, de 51 años.

2. La mujer estuvo manifiesta, aunque algo fortuitamente, expuesta a ovejas enfermas poco antes de comenzar sus síntomas.

3. Este es el tercer caso comunicado en que se diagnosticara la enfermedad antes de la muerte y el primero que sepamos en que se considerara el diagnóstico acertado antes de operar.

4. En este caso la afección parecía estar limitada al lóbulo inferior derecho al operar.

5. Los síntomas aparecieron aproximadamente siete años antes de la operación.

6. La iniciación fué insidiosa, caracterizándose por una tos seca que paulatinamente se volvió húmeda, y aparición tardía de dolor sordo sobre la zona afectada.

7. Los hallazgos radiográficos no fueron característicos de ninguna otra dolencia. La lesión no fué tal que produjera atelectasia, sino que, en contraposición a otros procesos inflamatorios, la zona comprometida permaneció esencialmente normal en tamaño.

8. La lobectomía no ha obtenido la curación, pues parece haber propagación de la enfermedad al resto del pulmón del lado operado a los siete meses de la intervención.

REFERENCES

(1) Wood, D. A., and Pierson, P. H.: Pulmonary adenomatosis in man, Am. Rev. Tuberc., 1945, *51*, 205.

(2) Lohlein, M.: Cystisch-Papillarer Lungentumor, Verhandl. d. deutsch. path. Gesellsch., 1908, *12*, 111.

(3) Sims, J. L.: Multiple bilateral pulmonary adenomatosis in man, Arch. Int. Med., 1943, *71*, 403.

(4) Obendorfer, S.: Zell-mutationen und multiple Geschwulstentstehungen in den Lungen, Virchows Arch. f. path. Anat., 1930, *275*, 728.

(5) Helly, K.: Ein seltener primarer Lungentumor, Ztschr. f. Heilk., 1907, *28*, 105.

(6) Bonne, C.: Morphological resemblance of pulmonary adenomatosis (Jaagsiekte) in sheep and certain cases of cancer of the lung in man, Am. J. Cancer, 1939, *35*, 491.

(7) Richardson, G. O.: Adenomatosis of the human lung, J. Path. & Bact., 1940, *51*, 297.

(8) Briese: Zur Kenntnis des primaren Lungenkarzinoms, mit statisischen Angaben, Frankfurt Ztschr. f. Path., 1920, *23*, 48.

(9) Bell, E. T.: Hyperplasia of the pulmonary alveolar epithelium in disease, Am. J. Path., 1943, *19*, 901.

(10) Taft, E. B., and Nickerson, D. A.: Pulmonary mucous epithelial hyperplasia (pulmonary adenomatosis): A report of two cases, Am. J. Path., 1944, *20*, 395.

(11) Paul, L. W., and Ritchie, G.: Pulmonary adenomatosis, J. Radiol., 1946, *47*, 334.

(12) Drymalski, G. W., Thompson, J. R., and Sweany, H. C.: Pulmonary adenomatosis, Am. J. Path., 1948, *24*, 1083.

FATAL TENSION PNEUMOTHORAX RESULTING FROM DIAPHRAGMATIC RUPTURE IN A PATIENT RECEIVING PNEUMOPERITONEUM[1]

S. A. YANNITELLI, C. E. WOODRUFF, E. E. MUELLER, AND W. L. HOWARD

(Received for publication March 21, 1949)

In recent years pneumoperitoneum with or without concomittant phrenic nerve interruption has attained considerable favor in the treatment of some types of pulmonary tuberculosis. The occasional complications that may occur such as air embolism, ascites, peritonitis, formation or aggravation of hernia, tear of peritoneal adhesion, mediastinal emphysema, atelectasis, diarrhea, gastric distress, and anorexia can be easily prevented with proper technique, or satisfactorily managed if they occur (1, 2). The purpose of the present paper is to report a fatal case of rupture of the diaphragm in a patient with pneumoperitoneum. To our knowledge, this complication has not been previously reported in the literature although Anderson and Winn refer to the possibility of rupture occurring as a result of an erosive, ulcerative tuberculous process of the diaphragm (3).

REPORT OF A CASE

D. D., a colored female, 16 years of age, was admitted to the Wm. H. Maybury Sanatorium on December 31, 1946 with a history of productive cough, night sweats, and weight loss for six weeks. Physical examination revealed a well-developed and well-nourished colored girl appearing chronically ill. Impaired percussion and bronchovesicular breath sounds were found over the upper third of the left lung along with an occasional post-tussic rale. Urine and blood examinations were essentially normal. Sputum tests were positive for tubercle bacilli. Chest roentgenogram on admission revealed a moderately advanced tuberculous process involving the upper two-thirds of the left lung with many small areas of rarefaction in this area. A roentgenogram taken four weeks after admission showed further progression of the disease (figure 1). Bronchoscopy on May 6, 1947 was essentially negative. The patient was carried on a conservative regimen of bed rest until May 9, 1947 when pneumoperitoneum was induced with the view of temporizing until the pneumonic character of the disease subsided. The pneumoperitoneum was induced and maintained without difficulty, resulting in an elevation of the left hemidiaphragm a maximum of two and one-half interspaces (from the tenth rib to the seventh interspace posteriorly) and the right hemidiaphragm two interspaces (tenth to eighth interspace). In October 1947 there was an increase in symptoms and a "spread" was seen in the base of the left lung, the right lung remaining clear. The patient received 84 Gm. of streptomycin from October 31, 1947 to January 22, 1948 with considerable symptomatic improvement. Pneumoperitoneum refills of 1,000 to 1,500 ml. of air were continued at weekly or ten-day intervals without difficulty, maintaining the diaphragms at the aforementioned levels (figure 2).

In February the possibility of surgical collapse was considered and on February 16, 1948 the refills were temporarily discontinued to allow some depression of the diaphragm so that better roentgenographic visualization of the involved lobes of the left lung could be obtained. On the afternoon of March 11, 1948, twenty days after her last refill, the patient noted rather sudden onset of mild subscapular pain aggravated by deep respiration but unaccompanied by dyspnea. She received sedatives and spent a comfortable night, having only slight pain the next morning. Roentgenographic examination at this time, however, revealed partial collapse of the right lung, with a small amount of fluid at the base. There was displacement of the heart and trachea to the left. The pneumoperitoneum was still present but it was considerably less than at the time of the last refill (figure 3). Careful

[1] From the Wm. H. Maybury Sanatorium, Northville, Michigan.

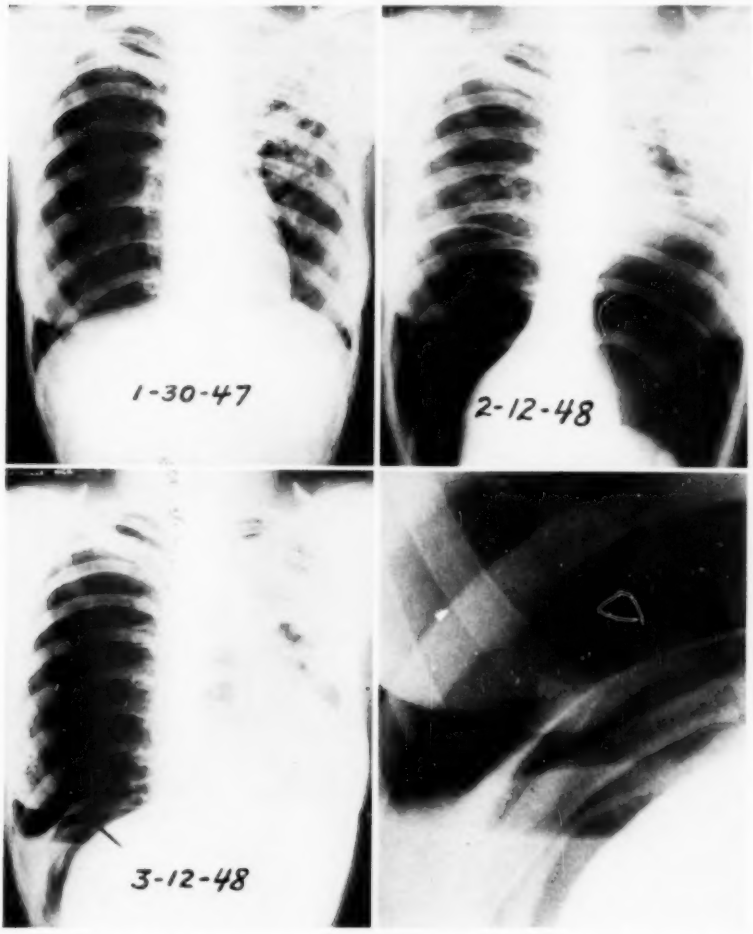


FIG. 1. (Upper left) Roentgenogram showing extent of disease before collapse therapy was instituted.

FIG. 2. (Upper right) Roentgenogram showing elevation of diaphragm following pneumoperitoneum.

FIG. 3. (Lower left) Roentgenogram showing first spontaneous pneumothorax. Arrow points to bleb-like shadows on pleural surface of diaphragm.

FIG. 4. (Lower right) Enlargement of blebs shown in figure 3.

examination of the roentgenogram revealed two adjacent, bleb-like shadows, each 7 mm. in diameter, projecting above the middle of the right leaf of the diaphragm (figures 3 and 4).

Air was aspirated from the right chest and the lung was allowed to re-expand. The

patient was started on a second course of streptomycin in an attempt to prevent complications. The pneumoperitoneum refills were then cautiously resumed to demonstrate whether or not a diaphragmatic rupture might be present. After small refills on April 5 and April 7, 1948, pressures in the peritoneal space were plus 4 and plus 6. A roentgenogram taken April 8 did not reveal any air in the right pleural space and the bleb-like shadows on the right leaf of the diaphragm were no longer visible (figure 5). During the next six weeks refills were continued and the previous elevation of the diaphragm was gradually attained. Since there was still no evidence of rupture, the pneumoperitoneum was continued as a therapeutic measure with moderate clearing of the pulmonary lesions during the next four months (figure 6).

On September 8, 1948 the patient received her usual refill of 1,300 ml. of air with initial pressures of plus 3, plus 5; and final pressures of plus 6, plus 8. Both diaphragms were well elevated (figure 6). During the day of September 16, it was observed that the patient was exceptionally boisterous, laughing, and moving about in bed considerably. At 9:30 that

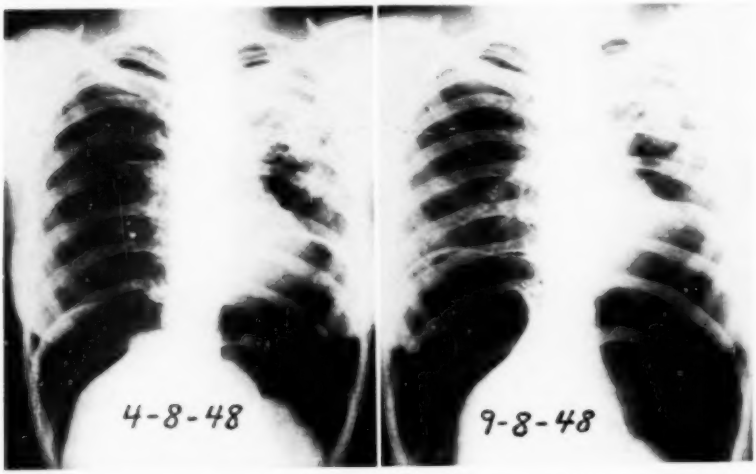


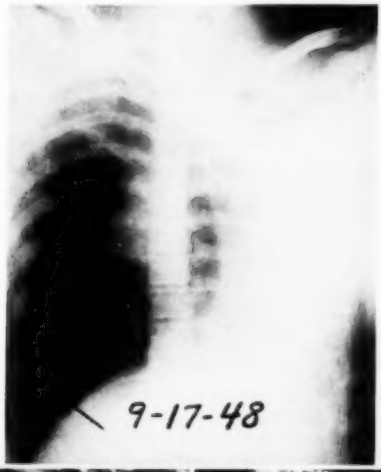
FIG. 5. (Left) Roentgenogram showing conditions when pneumoperitoneum was resumed

FIG. 6. (Right) Roentgenogram showing elevation of diaphragm immediately after last refill

evening she became somewhat apprehensive and complained of mild right shoulder pain for which she received sedatives. There was no noticeable dyspnea. At midnight her pulse rate was 92, respirations 24, and the patient appeared normal except for nervousness and mild pain. Additional sedatives were given. At 2:30 a.m. the patient raised a small amount of blood-streaked sputum. At 3:10 a.m. her respirations seemed more labored although the rate was 26 and pulse 100. The patient turned on her right side at 3:30 a.m. and was found dead at 3:50 a.m. A post-mortem roentgenogram was obtained (figure 7).

Post-mortem findings: Examination of the body revealed a well-developed and well-nourished colored girl appearing somewhat older than her stated age. Aside from pallor of the lips and mucous membranes, no external abnormalities were found. Before making any incision, a needle connected with a manometer was inserted through the right chest wall and a pressure of 14 cm. of water was registered. A free air space was not found when the needle was inserted through the abdominal wall. Upon opening the abdomen, the peritoneal surfaces appeared congested. Numerous small bubbles of air were found trapped behind the omentum. The right diaphragm was convex downward and reached the level of

the sixth rib anteriorly, the liver edge being pushed down 10 cm. below the costal margin. The left diaphragm was found at the level of the fourth rib. A second pressure reading of the right hemithorax, taken after the peritoneal cavity was opened, was 8 cm. of water.



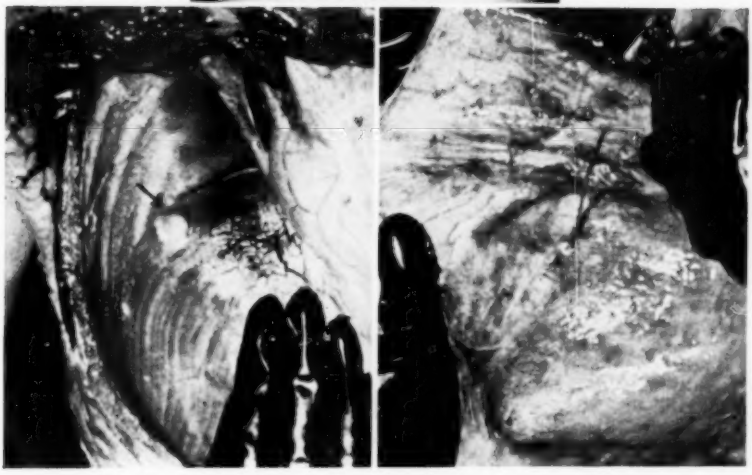


FIG. 7. (Top) Post-mortem roentgenogram. Arrow points to bleb on diaphragm.
FIG. 8. (Lower left) Post-mortem photograph. Arrow points to bleb on diaphragm.
FIG. 9. (Lower right) Post-mortem photograph showing probe passed through opening on peritoneal aspect of diaphragm.

Incision into the right chest permitted the rapid escape of air. The lower two-thirds of the right lung was found collapsed against the mediastinum which, in turn, was shifted considerably to the left. The upper third of the lung was only partially collapsed, being held in place by dense pleural adhesions present in this area. The right lung was red and

meaty in consistency. It was devoid of crepitation except in the apical region. No tuberculous lesions were found. The left lung showed small emphysematous areas in the apical region and in portions of the lower lobe. Much of the lung was dark red in color, completely devoid of air. On section, numerous old, caseous foci, varying in diameter from 2 to 15 mm., were found in the lower portion of the upper lobe and the adjacent portion of the lower lobe. These lesions were surrounded by atelectatic and partially fibrosed lung tissue.

A soft, whitish mass, 1.7 cm. in length and 0.7 cm. in diameter, which collapsed under pressure, was found projecting from the pleural surface of the right diaphragm. The mass was located in the middle portion of the diaphragm where the lateral muscle fibers join the central aponeurosis (figures 7 and 8). Pressure against the liver caused clear, yellow fluid to drip from the tip of the projection. On either side of the latter and several centimeters from it, small tags of fibrous tissue were found adhering to the diaphragm. These tags corresponded in position to similar tags found on the diaphragmatic surface of the right lung. On the peritoneal surface of the diaphragm was found a round opening, 2 mm. in diameter, which communicated with the bleb-like projection on the pleural surface. This opening lay between two diaphragmatic muscle bundles which appeared widely spaced in this area (figure 9). The remainder of the diaphragm was of usual thickness and structure.

The heart showed marked dilatation of the right ventricle. A persistent thymus weighing 60 Gm. was found. No other abnormalities of importance were found.

A histological section through the bleb on the diaphragm showed a hollow structure about 7 mm. in diameter. Its wall, about 1.0 mm. thick, was composed of a core of newly formed fibrous tissue with a granulomatous surface on either side. The layer of granulomatous tissue was heavier on the inside (continuous with the peritoneum) and, on this surface, a subacute inflammatory reaction was evident.

The immediate cause of death was given as tension pneumothorax and right-sided myocardial dilatation following rupture of the diaphragm.

DISCUSSION

Because of its unusual nature, some explanation of this case seems indicated. The first episode of tension pneumothorax caused considerable discussion as to whether this was the result of a rupture through the diaphragm or a "spontaneous" pneumothorax of the usual variety. The arguments for "spontaneous" pneumothorax were: (*1*) the relatively high frequency of this type of accident in patients with pulmonary tuberculosis as compared with the previously unheard-of occurrence of diaphragmatic rupture; and (*2*) the continued presence of pneumoperitoneal air immediately after the episode and its persistence even after the lung was completely re-expanded. The arguments favoring rupture of the diaphragm were: (*1*) the somewhat rapid decrease in size of the pneumoperitoneal air space; (*2*) the bleb-like shadows on the superior surface of the right hemidiaphragm; and (*3*) the lack of demonstrable tuberculosis in the patient's right lung which might conceivably have caused the usual type of "spontaneous" pneumothorax. After this first accident, thoracoscopy was considered to determine if a rent in the diaphragm actually existed but was dismissed in favor of further small pneumoperitoneum refills under careful observation. When no air was demonstrated in the right pleural space after these refills (figure 5), it was concluded that a diaphragmatic rupture was not present. In retrospect it seems evident that the opening in the bleb was closed by the organization of fibrin in the 25-day interval between the first accident and the time when the refills were resumed.

This case history presents other aspects which appear perplexing. Rupture through the diaphragm might be expected to occur during or immediately after a pneumoperitoneum refill when the intraperitoneal pressure is at a maximum, but in the present case the rupture did not occur until twenty and nine days, respectively, after the preceding

refill. It will be remembered that the patient's diaphragm was maintained at a fairly high level for ten months before her first episode of rupture. During this period the muscle fibers were apparently stretched apart sufficiently to permit a small rupture through the diaphragm, resulting in the formation of a bleb on its pleural surfaces. The work of Anderson (4) on the intrapleural pressure changes during pneumoperitoneum may indicate why this bleb ruptured so long after the previous refills were given. He demonstrated that intrapleural pressures were elevated immediately after a refill of pneumoperitoneal air and gradually readjusted to a normal pressure by the time the next refill was given. Therefore, although the highest intraperitoneal pressure is obtained immediately following a refill, the differential pressure between the intrapleural and intraperitoneal spaces may be greatest sometime later.

Two other factors should be mentioned as possibly precipitating the rupture of the bleb at such long intervals after the previous refills. As the diaphragm descended, the relationship of the bleb to the base of the right lung changed. This may have been sufficient to break a seal that had been established between these two structures. Secondly, it appears from the case history that the coughing, laughing, and boisterousness of the patient the evening before she died was an important factor in initiating the terminal episode of rupture. It is probable that the bleb was ruptured by the pull or tear of already stretched adhesions during this excessive activity of the diaphragm.

The plus 14 cm. of water pressure found in the right pneumothorax after death demands an explanation, since the maximum pressure ever reached in the peritoneal space during refills was only plus 8. It seems evident that the collapsible bleb on the pleural surface of the diaphragm acted as a valve while the diaphragm itself served as a pump forcing air through the valve. This pump-like action became more vigorous as increasing dyspnea caused greater respiratory effort. Thus a vicious cycle was established, the dyspnea produced by the partial collapse of the right lung increasing the action of the diaphragm which, in turn, pumped more air into the right pleural space creating further dyspnea.

It would seem that three main factors are pertinent in determining the seriousness of this complication of pneumoperitoneum: first, the size and suddenness of the rupture of the diaphragm; second, the volume and pressure of the pneumoperitoneum; and third, the valve effect that may occur which, associated with the pump-like action of the diaphragm, can set up a vicious cycle and result in a rapidly fatal course. These possibilities emphasize the need for careful observation of pneumoperitoneum cases since, if this complication occurs, early diagnosis and prompt treatment will be necessary to prevent a fatal outcome.

SUMMARY

A fatal case of rupture of the diaphragm and resulting tension pneumothorax in a patient receiving therapeutic pneumoperitoneum is reported. The autopsy findings and the pathological physiology involved are discussed along with factors that may determine the seriousness of this complication.

SUMARIO

Neumotórax Hipertensivo Letal Debido a Rotura Diafragmática en Paciente en Tratamiento con Neumoperitoneo

El caso letal comunicado es de rotura del diafragma seguida de neumotórax hipertensivo en paciente que recibía el neumoperitoneo terapéutico. Al discutir los hallazgos autópsicos y la fisiología patológica, menciónanse los factores que pueden determinar la gravedad de la complicación.

REFERENCES

(1) Mitchell, R. S., Hiatt, J. S., McCain, P. P., Easom, H. F., and Thomas, C. D.: Pneumoperitoneum in the treatment of pulmonary tuberculosis. Am. Rev. Tubere., 1947, *55*, 306.

(2) Trimble, G. H., Eaton, J. L., Crenshaw, G. L., and Gourley, I.: Pneumoperitoneum in the treatment of pulmonary tuberculosis, Am. Rev. Tubere., 1948, *57*, 433.

(3) Anderson, N. L., and Winn, W. D.: Pneumoperitoneum and diaphragmatic paralysis, Am. Rev. Tubere., 1945, *52*, 380.

(4) Anderson, N. L.: The rationale of therapeutic pneumoperitoneum, Dis. of Chest, 1948, *14*, 732.

TUBERCULOUS ARTERITIS OF THE ABDOMINAL AORTA WITH RUPTURE INTO THE THIRD PORTION OF THE DUODENUM

Report of a Case

HAROLD ZAROWITZ[1] AND DAVID M. GRAYZEL

(Received for publication April 25, 1949)

INTRODUCTION

Tuberculosis of the large arteries of the body has been of rare occurrence as evidenced by a review of the literature. The arteritis occurring in the small blood vessels is usually part of the tuberculous process that involves a particular organ and in itself is not very important, since it does not have any direct effect on the course of the disease. However, when the larger vessels are involved, a change in the immediate course of the disease ensues. In 1913, Haythorn (5) described four types of tuberculous arteritis. The first was miliary tuberculosis of the intima which he stated was the most common. In this type, miliary gl.stening tubercles were seen on the surface of the intima. The second consisted of polypi of tuberculous tissue attached to the intima. Here a small pear-shaped mass of tissue, which resembled a white thrombus, was attached by a pedicle to a slight elevation of the intima, with the distal portion swinging free in the direction of the blood current. The pathogenesis here consisted in deposits of tuberculous tissue on old sclerotic patches which were followed by thrombus formation over the area and which later became organized and assumed a polypoid mass. The third type was tuberculosis of the wall in which all the layers were involved, and the fourth type was aneurysm formation. According to Eppinger (4), aneurysms on a tuberculous basis are formed by mycotic emboli that enlodge in the vasa vasorum and cause a thrombosis which in turn results in an acute peri- and mes-arteritis with complete solution of the continuity of the elastica and damage to the adventitia with resulting aneurysm formation. However, aneurysms can also be formed by direct extension of a tuberculous process from within or from without.

The first case of a tuberculous aneurysm was reported by Kamen (6) in 1895. The patient was a soldier, 24 years of age, with chronic pulmonary tuberculosis and acute miliary tuberculosis. The former caused an aneurysm of the ascending aorta just above the aortic cusps by direct extension from caseating mediastinal lymph nodes.

Until 1933, 20 cases were reported of aneurysms of medium size and large arteries as a result of tuberculosis. Four of these were due to hematogenous dissemination with bacilli going through the vasa vasorum and lodging in the medial wall. There were no foci of tuberculosis surrounding these arteries. The primary source of the tuberculosis was known in all cases. The first of these cases was reported by Pel and recorded by Lenoble (7) in 1922. It was that of a 20-year-old female who died of an aneurysm of a femoral artery and the superior mesenteric artery, both of tuberculous origin. There were also tubercles on the mitral valve. The second report was that of Tozer (11) in 1915 and described a case in which a tuberculous aneurysm of the abdominal aorta ruptured into the duodenum. The third was that of Brockman (3) in 1926 in the case of an aneurysm of a femoral artery in a boy 14 years of age who also had Pott's disease. Brockman believed that this aneurysm occurred as a result of a mycotic embolus to the vasa vasorum of the femoral artery. The fourth case was that of Malcolm (8) in 1928, in which a 72-year-old male had a femoral aneurysm which ruptured. Miliary tuber-

[1] Jewish Hospital of Brooklyn, Brooklyn, New York.

culosis was found in this patient and tubercle bacilli were demonstrated in the media. All the coats of the arterial wall were necrotic. In 1933, Baumgarten and Cantor (2), reported a case of a 53-year-old male with an aneurysm of a femoral artery which ruptured. This was treated surgically and the histological study proved it to be of tuberculous origin. The patient was well three years after the rupture occurred. In this case no primary focus was demonstrated. In 1935 Barnard (1) demonstrated a case of a 63-year-old female with tuberculosis of the coronary and intracranial carotid arteries. Here, too, no primary focus was demonstrated. Thieme and Maddock (10) in 1939 reported a case of a 35-year-old male with peripheral vascular tuberculosis. There was no primary focus ever demonstrated. In 1941, Neel (9) described a case of a 21-year-old pregnant female with tuberculous thrombophlebitis in the lungs and tuberculous involvement of an external iliac artery. The lumen of the artery was filled with a caseous white thrombus and there were areas of inflammation and caseous necrosis in the intima and media with proliferation of connective tissue and vascular endothelium and infiltration by lymphocytes and epithelioid cells in the adventitia. Tubercle bacilli were demonstrated in the white thrombus.

Thus, tuberculosis of the large arteries occurring as a result of hematogenous dissemination is indeed a rare occurrence. We are now presenting a case of tuberculous arteritis of the abdominal aorta without aneurysm formation which occurred through hematogenous dissemination and precipitated rupture into the duodenum with immediate death.

REPORT OF A CASE

A. D., a 62-year-old white male was admitted to the Jewish Hospital because of continued fever, malaise, anorexia, and weight loss of six weeks' duration.

His past history was significant in that twenty years before admission he had suffered a coronary artery thrombosis from which he apparently had recovered completely. At the age of 18 he had one bout of hemoptysis which subsided within one week and for which no therapy was given. He had retired from business and during the past twenty years had occasional angina and exertional dyspnea.

Six weeks before admission he had an episode of fever and malaise which lasted for a few days. He was treated with sulfadiazine. Following this episode he never fully recovered. He noted anorexia, fatigability, and weight loss. Two weeks before admission he had a recurrence of fever and malaise. This did not respond to therapy and necessitated hospital observation.

The physical examination showed a well nourished and well developed adult male. The blood pressure was 150 systolic, 100 diastolic (mm. of mercury), pulse 130 per minute, temperature 100° F., and respirations 26 per minute. All findings were negative except for: (*1*) the heart was enlarged to the left by percussion and a soft apical systolic murmur was audible; (*2*)the liver was felt one and one-half finger-breadths below the costal margin; and (*3*) the spleen was felt one finger-breadth below the costal margin.

Two days after admission the patient appeared slightly dyspneic and cyanotic. Moist rales were audible at both bases and cleared slightly on coughing. A pericardial friction rub was heard in the second left intercostal space.

The urine showed a specific gravity of 1.022, albumin one plus, sugar zero, and 5 hyaline casts per high power field. The hemoglobin was 85 per cent, erythrocytes 4.10 million per cu. mm., total leukocytes 5,015 per cu. mm., with 85 polymorphunuclear leukocytes and 15 lymphocytes per 100 cells. The erythrocyte sedimentation rate varied from 9 to 12 mm (Westergren).

The following studies were normal: blood sugar, urea, uric acid, total protein, A/G ratio, prothrombin time, serum agglutination for typhoid, paratyphoid group, Brucella, Heterophile antibody titer, serum amylase, cerebrospinal fluid, and four blood cultures.

The following studies were abnormal: a glucose tolerance test showed a normal curve with a mild glycosuria; and an electrocardiogram showed slight depression of S T segment in Lead I and the Q wave in Lead III, a circulation time study (arm to tongue) was twenty seconds; and a sternal puncture showed "smudge" cells.

A gastrointestinal roentgenographic study revealed an esophageal hiatus hernia and multiple diverticula in the descending and sigmoid colon. A chest roentgenogram revealed that the heart was enlarged to the left and that both lung fields contained numerous stippled deposits scattered from apex to base.

Clinical course: The patient's temperature varied from 100 to 104°F. for the first week and the pulse rate varied proportionately. The respirations, however, varied from 30 to 45 per minute. He was given procaine-penicillin and streptomycin. During the second week the temperature varied from 99° to 101°F. From the fifteenth to the eighteenth day it varied from 100° to 101°F., and the respirations were normal for the last eleven days of admission. The patient requested that he be discharged on November 17, 1948.

At home he continued to have low-grade fever. He began to complain of aching pain in the lumbodorsal region and of lower abdominal cramp-like pain. The week before the second admission his temperature rose to 104°F. On December 11, he was readmitted to the hospital.

A physical examination showed the patient to be in no distress but "toxic" and pale. A loud pericardial friction rub was heard at Erb's point. A pulmonic systolic murmur was also noted. The liver was enlarged three to four finger-breadths below the costal margin and had a firm edge. The spleen was firm and nontender. It was noted that the abdominal aorta was easily palpable.

The following studies were normal: blood urea nitrogen, glucose, cholesterol, bilirubin, serum amylase, urine culture, urine, and cephalin flocculation tests. The erythrocyte sedimentation rate was 25 mm. per hour.

Clinical course (final admission): The temperature varied from 99° to 102°F. and the pulse and respirations were proportional. On admission he complained of severe abdominal pain. At times he became irrational. On December 18, at 5:30 p.m. it was noted that the patient had a fair day. At 8:50 p.m. he suddenly began to have gasping respirations and died ten minutes later.

Autopsy Findings

Lungs: The right lung weighed 600 Gm. and the left 550 Gm. The external surfaces were smooth and glistening, but on palpation small hard nodules up to 0.3 cm. could be felt subpleurally and deep within the parenchyma. The cut sections revealed frothy fluid that could be expressed on pressure. All the lobes were similar. The pleural surface over the left apex was slightly dimpled and was covered by thin fibrous pleural thickening. The lung tissue subjacent was firmer than the surrounding area. The bronchi were not unusual. The pulmonary arteries showed a mild degree of intimal sclerosis. The tracheobronchial lymph nodes were enlarged and soft. On cut sections they showed circumscribed areas of soft white and yellow tissue.

Gastrointestinal tract: The stomach contained large clots of blood. The duodenum and jejunum were filled completely with a similar material. In a third portion of the duodenum there was a perforation through the posterior wall which communicated with the lumen of the abdominal aorta (figure 1). In the duodenum, lying freely, was a round mass of tan, red, and brown tissue measuring 4 cm. in diameter which fit snugly into the perforation (figures 2 and 3).

Spleen: The spleen weighed 390 Gm. At one pole there was a yellow firm area which was depressed below the surface. The cut section showed this to be yellow and triangular in shape with its base at the surface of the spleen. The pulp was soft.

Kidneys: The right kidney weighed 200 Gm. and the left 220 Gm. The capsules stripped easily. The cortices were studded with small miliary white nodules which on cut section contained soft white material.

Lymph nodes: The lymph nodes in the area surrounding the aorta were not involved by a tuberculous process.

Pericardium: Both visceral and parietal pericardial layers were smooth and glistening and uninvolved by any pathologic process.

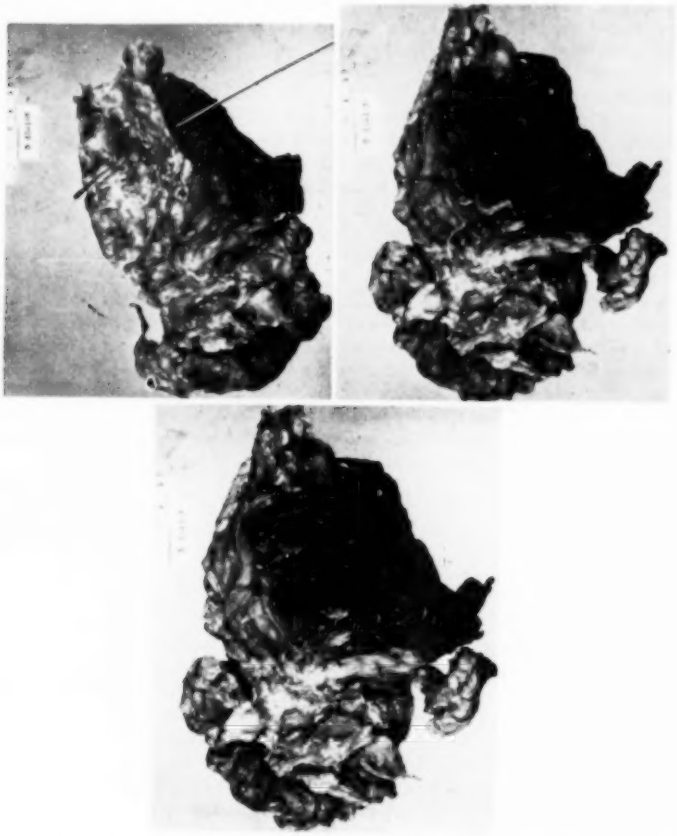


FIG. 1. (Upper left) Photograph showing probe passing from aortic lumen, on the left, into the darker duodenal lumen on the right.

FIG. 2. (Upper right) Photograph of perforation from the duodenal side.

FIG. 3. (Bottom) Photograph showing large clot occluding the perforation on the duodenal side.

Microscopic

Lung: In various parts within the interalveolar septa were found various-sized tubercles consisting of caseating, necrotic centers with Langhans' giant cells, epithelioid cells, and lymphocytes at the periphery. Some of the tubercles were located subpleurally. Some of the alveoli contained a homogeneous pink staining material. In the apex of the left lung there was a small tubercle adjacent to an area of ossification and fibrosis.

Liver: This showed small tubercles scattered throughout the lobules.
Adrenals: This showed one tubercle in the cortex and otherwise were not abnormal.
Prostate: This also showed one tubercle in the stroma and mild glandular overgrowth.

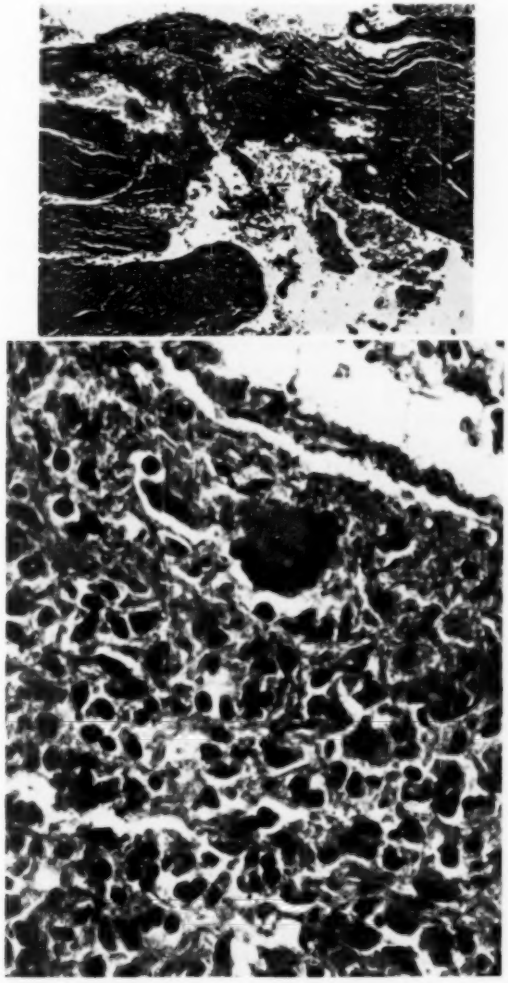


FIG. 4. (Top) Microphotograph showing dissolution of continuity of aorta by caseation.
FIG. 5. (Bottom) Microphotograph showing tuberculous reaction in adventitia with a Langhans' giant cell, lymphocytes and epithelioid cells.

Kidney: The cortices were studded with various-sized tubercles which were similar to those in the lung.
Spleen: This showed a large caseous infarct and many small tubercles within the parenchyma.

Aorta and site of perforation: The intima showed a large atheromatous plaque with many cholesterol clefts. The intima could be followed to a point where its continuity was interrupted by caseating, necrotic tissue. The continuity of the media and adventitia was also interrupted by similar material at the same point (figure 4). In these areas, especially in the adventitia, tuberculous granulation tissue consisting of Langhans' giant cells, epithelioid cells, lymphocytes, and fibrous tissue could be demonstrated (figure 5). A Ziehl-Neelsen histologic stain of these necrotic areas revealed the presence of a considerable number of acid-fast bacilli. There was no evidence of any aneurysm formation.

Anatomic diagnosis (partial): Tuberculosis, miliary, of lungs, liver, kidney, spleen, prostate, adrenal and tracheobronchial nodes.

Tuberculous arteritis of abdominal aorta with rupture into third portion of duodenum with hemorrhage.

Apical tuberculosis, old; left, with ossification.

COMMENT

It has been demonstrated that this case of tuberculous arteritis occurred through hematogenous dissemination, in as much as there were no tuberculous foci in the tissues surrounding this portion of the aorta and since it was directly associated with acute miliary tuberculosis. There are two possibilities as to how the invasion of the wall could have occurred. The first is that mycotic emboli entered through the vasa vasorum and precipitated the arteritis. The second is that these same emboli could have implanted themselves upon an ulcerated atheroma of which there were many in this portion of the aorta. From here the invasion would be from within out. However, it is impossible to say which was the basic mechanism of invasion.

It is interesting to note that this is the only reported case in which aneurysm formation had not occurred.

The primary focus in all probability was the old tuberculous lesion found in the apex of the left lung, although no definite evidence of activity could be domonstrated.

This case further bears out the fact that tuberculosis of large arteries usually changes the immediate course of the disease.

SUMMARY

A case of tuberculous arteritis of the abdominal aorta with rupture into the duodenum is reported. The lesion was associated with generalized miliary tuberculosis which presumably arose from an old pulmonary tuberculous lesion. The arteritis was not associated with the formation of an aneurysm.

SUMARIO

Arteritis Tuberculosa de la Aorta Abdominal, con Rotura en la Tercera Porción del Duodeno

La tuberculosis de las grandes arterias es rara.

Ofrécense un repaso de la literatura y un caso de arteritis tuberculosa de la aorta abdominal con rotura intraduodenal.

No había formación de aneurisma.

Esta lesión se asocia a granulia, y se discute la patogenia.

Se da por sentado que el foco primario radica en una antigua lesión tuberculosa en el pulmón.

REFERENCES

(1) Barnard, W.: Tuberculous arteritis; J. Path. and Bact., 1935, *40*, 433.
(2) Baumgarten, E. C., and Cantor, M. O.: Tuberculous mesarteritis with aneurysm of femoral artery, J. A. M. A., 1933, *100*, 1918.
(3) Brockman, E. P.: Aneurysm of the femoral artery in a patient with Pott's Disease, Brit. J. Surg., 1926, *14*, 671.
(4) Eppinger, H.: Pathogenesis der Aneurysmen, Arch. f. klin. Chir., 1887, *35*, Supp. 156.
(5) Haythorn, S. R.: Tuberculosis of the large arteries, J. A. M. A., May 10, 1913, *60*, 1413.
(6) Kamen, L.: Aortenruptur auf Tuberculous Grundlage, Beitr. z. path. Anat. u. z. allg. Path., 1895, *17*, 416.
(7) Lenoble, E.: Arch d. mal du coeur. October, 1922, *15*, 677.
(8) Malcolm, R. B.: Tuberculous artery of the right femoral artery with miliary tuberculosis, Canad. M. A. J., 1928, *19*, 33.
(9) Neel, W., and Herrmann, L. G.: Peripheral arteritis with tuberculous thrombophlebitis in lungs, Am. Heart J. 1941, *22*, 702.
(10) Thieme, T., and Maddock, W. G.: Primary tuberculous peripheral vascular disease, Surgery, 1939, *6*, 604.
(11) Tozer, E. A.: Arch. d. mal du coeur, July 1928, *8*, 312.

Addenda

Since this paper was written, four other articles on tuberculous aneurysm of the abdominal aorta have come to the authors' attention:

(1) Scott, J. W.: Am. Heart J., April 1949, *37*, 820.
(2) Bagozzi, U.: Arch. ital. di anat. e istol. pot. 1931, *2*, 1189.
(3) Pomerantz, R. B.: Am. Heart J., 1949, *37*, 142.
(4) Owens, J. N., and Bass, A. D.: Arch. Int. Med., 1944, *74*, 413.

Letters to the Editors

THE CHEMOTHERAPEUTIC ACTION OF STREPTOMYCIN PARA-AMINOSALICYLATE IN EXPERIMENTAL TUBERCULOSIS IN MICE

To the Editors of the American Review of Tuberculosis:

Lehmann in 1946 (Lancet, 1946, *1*, 15) called attention for the first time to the tuberculostatic action of paraaminosalicylic acid *in vitro* and to its suppressive effect on the course of tuberculous infection in animals and man. Since then, many reports on the antituberculous activity of this substance have appeared (See Proc. Staff Meet. Mayo Clin., 1949, *24* (13), 342). Studies to date have emphasized: (*1*) the large dosages of para-aminosalicylic acid necessary in order to influence the course of the infection when the oral route of administration is used; and (*2*) the frequent gastrointestinal disturbances resulting from the administration of these large doses.

In 1947, Youmans and his associates (J. Bact., 1947, *54*, 409) called attention to the possible synergistic effect of para-aminosalicylic acid on the action of streptomycin when the two tuberculostatic agents are used in combination. Preliminary clinical studies have been carried out since that time to study this synergistic action, and data are available to suggest that the administration of para-aminosalicylic acid in conjunction with streptomycin lowers the incidence of the emergence of streptomycin-resistant strains of tubercle bacilli (See Report of the Seventh Streptomycin Conference held by the U. S. Veterans Administration, Army, and Navy, April 1949). Large dosages of para-aminosalicylic acid (8 to 15 Gm. per day) have been used, however, throughout the studies.

The para-aminosalicylic acid salt of streptomycin is a highly purified compound consisting of 56 parts of streptomycin and 44 parts of para-aminosalicylic acid. One molecule of pure streptomycin base combines with 3 molecules of para-aminosalicylic acid (4-aminosalicylic acid) to form the water-soluble salt, streptomycin para-aminosalicylate. It has a molecular weight of 1,039 and a theoretical potency of 558 γ of pure streptomycin base per mg. total weight of salt. Preliminary studies of the tuberculostatic activity of this salt (Hobby *et al.*, Report of the Seventh Streptomycin Conference held by the U. S. Veterans Administration, Army, and Navy, April 1949) have indicated that it is approximately twice as active *in vitro* as streptomycin alone when compared on a streptomycin unitage basis. Streptomycin-resistant variants of *M. tuberculosis* may or may not be sensitive to this salt; all are more sensitive to it, however, than to streptomycin sulfate (see table 1).

In vitro studies to demonstrate the emergence of strains resistant to streptomycin para-aminosalicylate have failed to show such mutants during a three months' study. It is recognized that this does not mean that such resistant organisms will not appear under appropriate conditions. The data available suggest, however, that the incidence with which strains resistant to this salt will appear is low.

Streptomycin para-aminosalicylate may be administered without difficulty to animals and man. This salt permits the administration of streptomycin and para-aminosalicylic acid simultaneously in a single injection. Its activity *in vivo* is, therefore, of interest.

A study of the chemotherapeutic action of streptomycin para-aminosalicylate in

comparison to that of streptomycin sulfate was carried out in mice infected intracerebrally with the H37Rv strain of *M. tuberculosis*. The results of this study indicate that the para-aminosalicylic acid salt of streptomycin, in dosages equivalent to 400 γ of pure streptomycin base, is more effective than the same quantity of streptomycin sulfate. This effect may be evidenced by comparison of both the average survival time and the actual per cent survival at the end of the observation period (see table 2).

TABLE 1

The In Vitro Tuberculostatic Activity of Streptomycin Para-aminosalicylate

CULTURE	SENSITIVITY: (γ PURE STREPTOMYCIN BASE PER CC.)	
	Streptomycin Sulfate	Streptomycin-PAS
H37Rv	0.5	0.23
Variants (H37Rv)		
7 strains	>10,000	1,163–2,325
1 strain	6,000	930
1 strain	1,250	<9.3
Freshly Isolated		
3 strains	<1	0.23–0.50
2 strains	2–10	0.90–8.0
1 strain	25	7.4
2 strains	>100	<1.9 –29.3
1 strain	5,000	10.0

Sensitivity = least amount necessary to inhibit growth at the end of 12 days' incubation in Dubos liquid media.

TABLE 2

The Chemotherapeutic Activity of Streptomycin Para-aminosalicylate in Experimental Tuberculosis in Mice

(Strain H37Rv)

THERAPY		PER CENT SURVIVAL MONTHS				AVERAGE SURVIVAL TIME, DAYS CALCULATED AT: (MONTHS)			
Agent	Dosage SM γ/day	1	2	3	4	1	2	3	4
SM-PAS	400	100	100	90	90	30	60	89	114
SM-SO_4	400	60	50	40	40	28	43	57	72
Controls	—	70	30	30	10	29	41	50	61

All animals in this experiment were treated for one month only. The number of animals used was small (10 per dosage). Repeated experiments on large numbers of animals, however, have shown comparable results.

The para-aminosalicylic acid salt of streptomycin is nonirritating in animals upon repeated injection at the same site. It possesses the same degree of acute toxicity for lower animals as does the calcium chloride double salt of streptomycin. Chronic toxicity studies in cats indicate that the toxicity of the PAS salt of either streptomycin or dihydrostreptomycin should be the same in man as that of streptomycin or dihydrostreptomycin, respectively.

By injection the small amount of para-aminosalicylic acid present in this compound appears to be sufficient to alter the course of tuberculous infection in mice. The true value of this salt, however, will depend upon whether or not the amount of para-aminosalicylic acid present is sufficient to alter the incidence of emergence of streptomycin-resistant strains of *M. tuberculosis* in man. This can be determined by clinical trial only, and studies are in progress to determine the rate of absorption of streptomycin para-aminosalicylate, its therapeutic value, toxicity, and ability to prevent the emergence of streptomycin-resistant organisms in tuberculous individuals.

G. Hobby
P. Regna
T. Lenert

Biological and Chemical Research Laboratories
Chas. Pfizer & Co., Inc.
Brooklyn, New York
October 13, 1949.

THE EFFECT OF ANTIHISTAMINE MEDICATION ON THE TUBERCULIN REACTION

To the Editors of the American Review of Tuberculosis:

I have read with considerable interest the article in the September 1949 number of the *American Review of Tuberculosis* by Doctors Friedman and Silverman on "The Effect of Antihistamine Medication on the Tuberculin Reaction in Children." In the light of my own experiences with antihistaminic drugs, I am certain that the results of their study are rendered delusive by several factors: first, by inferring at the outset the relationship of the skin reaction to histamine and other allergens, such as ragweed and timothy, to the skin reaction in an individual hypersensitive to tuberculin; second, by expecting to see results with " homeopathic" doses of antihistamine used for only four days (even the ten children given large doses received the drug for only two days prior to the skin test and for two days thereafter); third, the tests were run on children from five to eleven years old. In children of this age group the degree of hypersensitivity is less than that seen in young adults and older humans.

In a series of cases of various types of tuberculosis in which antihistaminics were employed to study both the effects on the Mantoux test and the tuberculous lesions, reported in *Annals of Allergy*, May–June 1949, 7, 306, we found some very interesting results when adequate dosage and time were also employed. When 500 milligrams of drug are given for six months with pulmonary and other forms of tuberculosis, one begins to see the results that cannot possibly be seen by employing 60 milligrams for four days. In 24 of the 30 cases reported, the Mantoux (using PPD, first strength) was converted gradually to negative and remained negative, except for a few instances, for the duration of the antihistaminic therapy. All skin tests returned positive within four weeks after medication was discontinued. Some very interesting effects on pulmonary lesions, some quite dramatic, are also demonstrated.

However, it is quite unfair to correlate visceral (pulmonary) hypersensitivity with the state of the skin reaction and, therefore, the degree of visceral response cannot be correlated with the degree of skin response to antihistaminics. This is apparently true in all forms of allergy. Actually, the skin test with any allergen is a pretty poor index of hypersensitivity elsewhere. This is one important fallacy in the usual skin tests for allergies.

I cannot agree that, as the authors state, the therapeutic effectiveness of the various antihistaminics are quite similar. Anyone with hay fever will quickly disagree with that statement, but also we found in our intensive studies that a change to one other antihistamine in the group of drugs employed would sometimes bring about a change in the Mantoux or lesion which the other antihistaminic was, to all appearances, incapable of producing in that particular patient. Patients with allergies are often benefited by one and not by another of the antihistaminics and, as well, will become refractive to one drug after a time, and not to another.

I sincerely hope that this criticism will tend to make those who plan to use antihistaminics and other drugs experimentally more aware of the importance of adequate time and dosage in the proper evaluation of the results. Bacterial allergy is probably an important factor in all infections, and experimentation along these lines is now being carried on in a number of laboratories and institutions. It is extremely important now that a plea be made for very careful evaluation of methods used and results obtained. This especially applies to time and dosage.

ALFRED R. HENDERSON

MEMPHIS, TENNESSEE
OCTOBER 3, 1949

BRUCE H. DOUGLAS
1892-1949

Bruce H. Douglas

1892-1949

Bruce Douglas lost his life in an automobile accident August 11, 1949. Quiet, kindly, thoughtful, wise, humble Bruce Douglas! His death leaves a large void in three areas of activity—in tuberculosis and public health within his chosen profession, and in religion—for in each of these he established himself as a leader and counsellor of first water.

Doctor Douglas was born in Des Moines, Iowa, on August 26, 1892, the son of John Henry, Jr., and Mabel Hutchinson Douglas. In 1915 he was graduated from Whittier College, California, where he was a member of the baseball team. Following then in order were his M.D. degree from Rush Medical College of the University of Chicago, internship at Harper Hospital, Detroit, and assistant residency at Herman Kiefer Hospital where he began a career in tuberculosis work in which he became preeminent. Shortly after he transferred from Kiefer to the Maybury Sanatorium (also operated by the Detroit Department of Health) his capacities brought him to the superintendency of the latter institution. He had held this position for ten years when he relinquished it to become Controller of Tuberculosis of that city. His eight years as Controller set many examples for the country, for the Detroit campaign against tuberculosis was exceptionally active and fruitful. From this position it seemed but a natural and logical move that he should succeed to that of Commissioner of Health of that city upon Doctor Henry Vaughan's resignation. At the time of his tragic death he ranked among the leading health officers of the nation.

As president of the American Trudeau Society in the year, in Boston, when the new constitution was adopted, he evoked the admiration of all by the remarkable manner in which the day-long session was conducted. All were impressed with what adroitness and eminent fairness the chairman of the day presided over the discussions, many of them featured by feeling and heat. Few knew that he had anticipated the need of complete familiarity with parliamentary usage and characteristically had perfected himself in it beforehand.

From 1939 to the time of his death, Doctor Douglas served as a member of the Board of Directors of the National Tuberculosis Association, doing faithful work on numerous committees the while. He was a member of the Executive Committee in 1939 and 1940, and the Association elected him president for the year 1941–1942. Doctor Douglas was a member of the Editorial Board of the American Review of Tuberculosis from 1938 to 1947.

From 1941 he served as Professor of Preventive Medicine and Public Health in the School of Medicine, Wayne University, and as Lecturer on Public Health in the School of Public Health of the University of Michigan. He was a certified specialist in the American Board of Internal Medicine, a fellow in the American College of Physicians, American Association for the Advancement of Science, American Public Health Association, and American Medical Association. He held membership in numerous other national and local associations and was on

the governing boards of several medical, philanthropic, and social organizations of both national and local scope. During World War I he was a private and in the last war was Surgeon, United States Public Health Service Reserve Corps.

His scientific contributions to our expanding knowledge of tuberculosis and public health have been marked for their quality and range.

Born into the Society of Friends, this "quiet Quaker" lived and exemplified a fine philosophy of life. He was interested in human behavior and was wise. His counsel was often sought. Whether the appeal came from the American Friends Service Committee, the Interracial Commission of Detroit, a staff of physicians with a problem from the sickroom, an auditor from the Budget Bureau, or an irate citizen with a grievance, his reaction and advice always seemed to be born of wisdom and understanding.

Always soft spoken, unaffected by his success, and approachable if sometimes almost shy, he was friend to everyone. He was capable of prodigious effort and work yet never appeared to be hurried, for there was always abundant time for any who wanted to see him. His daily life was the embodiment of unselfishness, and perhaps his most outstanding personal trait was humility. In the days of the depression and later of the war, he spent endless hours over adjustments, and, with steadfast devotion, was attentive to the unmet needs of patients and employes. His trials he met with remarkable serenity and rare wisdom. He achieved eminence but maintained humility. He was a good man—good without smugness—and, I think, the best and kindliest man I have known.

Bruce Douglas is dead. The depressing significance of the fact bears down upon those who knew and loved him and those who depended upon him for advice, help, and interest. But his life was an extraordinarily useful one. He leaves his family a splendid heritage; and all, a worthy example.

H. S. Willis

BOOKS

H. McLeod Riggins and H. Corwin Hinshaw (Editors): *Streptomycin and Dihydrostreptomycin in Tuberculosis. Pp. xvii-554, National Tuberculosis Association, New York, N. Y., 1949, cloth, $7.50.*

This volume of 554 pages is composed of 33 papers on various aspects of streptomycin and tuberculosis, grouped for convenience under eight major headings, including historical aspects of the subject, the relation of the American Trudeau Society to early studies, bacteriological and pathological aspects of the problem, detailed and summarizing reports on the clinical experience of Trudeau Society investigators, experimental and clinical studies on dihydrostreptomycin, and, finally, investigations of combined therapy, with emphasis on the adjuvant effect of para-aminosalicylic acid in treatment. Sixteen, or approximately one-half of the papers, are reprints of previous publications. These include three of the original classics on the subject, viz., the paper by Schatz and Waksman giving the first detailed report on the effect of streptomycin on the tubercle bacillus, and the two well-known papers by Feldman and Hinshaw describing the first tests of the value of streptomycin in the treatment of tuberculosis in experimental animals and man. The other seventeen papers represent original contributions, the majority of which are an outgrowth of a carefully planned therapeutic trial program on the clinical value of streptomycin organized in 1946 by a group of clinical and laboratory investigators in the Trudeau Society.

The volume was planned originally as a report to the six streptomycin producers who made the study possible by contributing enough streptomycin, at a time when the drug was very costly, for the treatment of 1,000 tuberculous patients. During the course of preparation of this report such great development of the subject occurred that it appeared highly advantageous, in the interest of a broad understanding of the value of streptomycin in the treatment of tuberculosis, to supplement the individual and summarizing reports by members of the Trudeau Society group with papers resulting from other important research, much of which, like the studies of the Tuberculosis Study Section of the Research Grants Division of the National Institute of Health, was stimulated by the Trudeau Society investigation. The volume includes reports of work sponsored by these two groups, a summary of results of a very extensive cooperative streptomycin program of the Veterans Administration, U. S. Army, and U. S. Navy, and two papers sponsored in part by the Committee on Chemotherapeutics and Other Agents of the National Research Council. It is interesting to note that certain of the investigators submitting reports in this volume were actively concerned in the programs of all of these organizations. Thus the volume as a whole represents a remarkable combination of experience.

The bacteriological and pathological papers present fundamental data fur-

nishing a convenient source of information on a multitude of problems in these fields. Included are accounts of the sensitivity and resistance of tubercle bacilli to streptomycin and the histological character of the effect of streptomycin on tuberculous lesions in animals and man. In this section is a fine paper also by Feldman on critical evaluation of a chemotherapeutic agent through animal experimentation.

The chief interest of the general reader will be focused on the Summary Report of the Streptomycin-Tuberculosis Research Project of the Trudeau Society. In the analysis of clinical data from the cooperative enterprise, the editors had the able assistance of Dr. Carroll E. Palmer and Mrs. Shirley H. Ferebee, of the Field Studies Section, Tuberculosis Division, Public Health Service. A series of charts in this section, which deal specifically with the value of different regimens of streptomycin, indicate that streptomycin is of greatest efficacy in acute forms of tuberculosis; that large daily doses, although more toxic, are definitely more effective than small doses; that the development of drug-fastness of infecting tubercle bacilli is directly related to the length of treatment; and that relapse of the disease after treatment increases with the passage of time, a fact emphasizing the necessity of supplementing streptomycin treatment with other therapeutic measures of established value.

The six papers on dihydrostreptomycin included in the volume are reprints of the well-known series which appeared in the *American Review of Tuberculosis* in November 1948. More than any others these papers point up the difficulty of keeping abreast of developments in a rapidly expanding field through the medium of monographs like this one. The current principal questions on the place of dihydrostreptomycin remain unanswered, because they arose too recently for inclusion.

The final section is in the field of apparent greatest promise, combined therapy. The volume closes on a note of optimism cautiously expressed, on the effect of para-aminosalicylic acid in delaying the emergence of streptomycin-resistant strains of tubercle bacilli.

The volume will be of great value to practicing clinicians and investigators alike. Although loosely organized, as a result of change in its objective in the actual course of its preparation, it loses little of its usefulness thereby, for its chief and lasting value will be as a reference source book in the many fields covered. It is reasonable to expect that its value for the therapeutic results described and the expert analyses based upon them will be ephemeral, for the results of much larger studies, well supported by critical analysis, may be expected in the near future. The volume is timely at present, however, and furnishes a remarkable picture of cooperation in a clinical investigation. The summaries and analyses of results of investigation interspersed throughout the book illustrate clearly the value and also the limitations of the extraordinary drug on which the book is based. Great credit is due the editors and publishers in making such a compilation possible.

ESMOND R. LONG

LARS WERKOE: *The Influence of Positive Pressure Breathing on the Circulation in Man, Acta medica Scandinavica, Stockholm, Sweden, 1947.*

This is a short monograph describing the effects on the circulation of various forms of positive pressure breathing; specifically, artificial respiration by intermittent (inspiratory) positive pressure, spontaneous respiration under continuous positive pressure, and spontaneous respiration against expiratory positive pressure. Most of the work was concerned with inspiratory positive pressure breathing (IPB); several artificial respirators designed by the U. S. Army Air Forces were used. The research was done by the author at Bellevue Hospital, New York City, in collaboration with Cournand and associates.

After a review of the literature, a detailed description is given of the methods employed in the author's work, including the technique of right heart catheterization, the determination of cardiac output, and the recording and analysis of peripheral arterial and of right heart and pulmonary arterial pressures.

The subjects studied consisted of fourteen individuals with normal circulation and twelve with various forms of cardiovascular disease, some compensated, others in failure. In the subjects with normal circulation, intermittent positive pressure breathing caused increased arterial blood pressure and increased mean and diastolic pressures in the right ventricle and pulmonary artery, proportional to the applied mean mask pressure, but usually less than the applied pressure. When the mean mask pressure exceeded plus 5 mm. of mercury, the cardiac output decreased significantly, and in proportion to the height of the mean mask pressure. Mean mask pressures in the region of plus 12 mm. of mercury caused decrease in cardiac output of about 30 per cent. Total peripheral resistance increased with increasing mask pressure in the systemic circuit, and usually in the pulmonary circuit.

Further analysis of these results was made in three subjects in whom pleural pressures were recorded in addition to the other measurements. During the positive pressure inspiratory phase, right auricular and right ventricular diastolic pressures increased, but less than the increase in pleural pressure. Right heart filling was thus decreased, which was interpreted as indicating that right heart output was also decreased. Left ventricular output, on the other hand, was considered to be increased during positive pressure inspiration, due to the forcing of additional blood from lungs into the left heart. During expiration, net filling pressure in the right heart (diastolic right ventricular pressure minus pleural pressure) was increased, indicating increased cardiac output. Evidence for this interpretation was provided by the facts that the average net filling pressure in the right ventricle for the whole respiratory cycle was found to change proportionally to the changes in cardiac output, and that the greater the number of beats during the respiratory cycle, that occurred with low filling pressures, the greater the decrease in cardiac output. The suggestion was made that, when intermittent positive pressure breathing is used for artificial respiration, the inspiratory period should be short and the expiratory period long, to avoid decreasing the cardiac output.

In one patient with heart failure, positive pressure breathing, producing decreased filling pressure in the right ventricle, resulted in an increased cardiac output.

A finding of special interest, outside the pressure breathing studies, was that in normal subjects breathing 10 per cent oxygen at normal or atmospheric pressure there occurred a definite rise in pulmonary artery pressures.

Expiratory positive pressure breathing caused only small changes in blood pressures and cardiac output. In one case, continuous positive pressure breathing with a low mean mask pressure resulted in a reduced cardiac output and increase in arterial right ventricular and pulmonary artery pressures.

DICKINSON W. RICHARDS, JR.

INDEX OF SUBJECTS AND AUTHORS

ACKERMAN, HELEN. See CARPENTER, CHARLES M., *et al.*

Activity, antituberculous, of natural or synthetic compounds, 90, 109, 121

Adenomatosis, alveolar, 788

——, pulmonary, 258, 788

Agents, tuberculostatic, guinea pig test for, 223

AKAWIE, SHIRLEY. See DUNN, KATHARINE REMINGTON, *et al.*

——. See DUNN, MAX S., *et al.*

ALBRECHT, F. KENNETH. What's wrong with mass X-ray surveys? (Letters to the Editors), 532

Allergens, acid-fast, Use of biometric methods in comparison of, 131

Allergy, tuberculin, subsequent to BCG vaccination in guinea pigs, 547

AMERICAN TRUDEAU SOCIETY: Statement on BCG, 681

AMILL, LUIS A. See JONES, OSWALD R. *et al.*

Amines, aliphatic, effect of, on ability of virulent mycobacteria to bind neutral red (Letters to the Editors), 384

Amino Acids, Urinary excretion of, in normal subjects, 439

——, —— —— in tuberculous subjects, 448

Aneurysms, Rasmussen's, 589

Anorexia, Insulin treatment of tuberculous patients with, 25

Antihistamine medication, Effect on tuberculin reaction (Letters to the Editors), 811

—— —— —— —— —— —— in children, 354

Antituberculous agents in chicks, Evaluation of, 366

Aorta, abdominal, Tuberculous arteritis of, 801

Arteritis, tuberculous, 801

AUERBACH, OSCAR. Tuberculosis of the trachea and major bronchi, 604

Aureomycin, tuberculostatic activity of, *in vitro* and *in vivo*, 143

Auscultation, 639

Autolytic tuberculin tests in children, Transcutaneous, 45

Avian tuberculosis. See Tuberculosis, avian.

AYVAZIAN, FRED, AND BADGER, THEODORE. Tuberculosis in nurses: Clinical observations on its pathogenesis as seen in a fifteen-year follow-up of 745 nurses, 305

Bacilli, tubercle, Self-injection of, 514

—— ——, Toxicity of sputum digestants to, 628

Bacillus, tubercle, slide culture method for detection and observation of growth of, 51

BADGER, THEODORE L., AND AYVAZIAN, FRED. Tuberculosis in nurses: clinical observations on its pathogenesis as seen in a fifteen-year follow-up of 745 nurses, 305

BARCLAY, WILLIAM R. The intravenous administration of p-aminosalicylic acid (Letters to the Editors), 385

BASS, H. E., AND WORTMAN, H. C. Abdominal pneumocele following artificial pneumoperitoneum, 520

BCG vaccination, cutaneous, in guinea pigs, 547

—— ——, Immunological aspects of (editorial), 670

——, —— in duration of tuberculin skin sensitivity after, 541

BERARD, LEROY. See SWEANY, HENRY C., *et al.*

BERNSTEIN, J., and DONOVICK, R. On the action of thiosemicarbazones in experi mental tuberculosis in the mouse(Let ters to the Editors), 539

BERRY, J. W., AND LOWRY, HOPE. A slide culture method for the early detection and observation of growth of the tubercle bacillus, 51

Beryllium exposure, pulmonary granulomatosis after, 755

BHATTACHARYA, B. K. See SMITH, M. I., *et al.*

BINKLEY, FREDERICK M. See SHIPMAN, SIDNEY J., *et al.*

Biometric methods, Use of, in comparison of acid-fast allergens, 131

BIRKHAUG, KONRAD. Correlation of numbers of cutaneous BCG vaccination papules and subsequent tuberculin allergy and tuberculosis resistance in guinea pigs, 547

BLADES, BRIAN B., AND MEADE, RICHARD H., JR. The surgical treatment of recurrent and chronic spontaneous pneumothorax of nontuberculous origin, 683

Boeck's sarcoid, Pathological and experimental studies of, 236

BOOKS:

BROWN, ESTHER LUCILE. Nursing for the Future: A Report Prepared for the National Nursing Council, 390

COOPE, ROBERT. Diseases of the Chest, 390

FRANCIS, JOHN. Bovine Tuberculosis: Including a Contrast with Human Tuberculosis, 389

HERTZBERG, GERHARD. The Achievements of BCG Vaccination, 675

HILL, A. BRADFORD. Principles of Medical Statistics, 147

MALMBERG, CARL. 140 Million Patients, 678

RIGGINS, H. MCLEOD, AND HINSHAW, H. CORWIN. Streptomycin and Dihydrostreptomycin in Tuberculosis, 815

SANCHIS-OLMOS, VICENTE. Skeletal Tuberculosis, 145

SAND, RENÉ. Vers la médicine sociale, 146

WERKOE, LARS. The Influence of Positive Pressure Breathing on the Circulation in man, 817

WILLIS, R. A. Pathology of Tumors, 144

BREWER, LYMAN A., III, AND DOLLEY, FRANK S. Tumors of the mediastinum: A discussion of diagnostic procedure and surgical treatment based on experience with forty-four operated cases, 419

—, WILMA D., CEDERQUIST, DENA C., STRINGER, C. J., AND OHLSON, MARGARET A. Studies of food intake and requirements of women with active and arrested tuberculosis, 455

Bronchi, Major, Tuberculosis of, 604

——, ——, —— Streptomycin in treatment of, 32

BUGIE, ELIZABETH J. See SOLOTOROVSKY, MORRIS, *et al.*

CAMERON, VIRGINIA. The cost of research on tuberculosis in the United States. Analysis of allocations in 1947–1948, 393

CAMIEN, MERRILL N. See DUNN, KATHARINE REMINGTON, *et al.*

——. See DUNN, MAX S., *et al.*

CARPENTER, CHARLES M., STOKINGER, HERBERT E., SUHRLAND, LEIF G., AND ACKERMAN, HELEN. Chemotherapy of murine leprosy, 359

CEDERQUIST, DENA C. See BREWER, WILMA D., *et al.*

Chemotherapeutic studies of new sulfones and streptomycin in experimental tuberculosis, 62

Chemotherapy of murine leprosy, 359

Chest photo-roentgenography, routine, 377

Chicks, Avian tuberculosis in, 366

Children, Tuberculin reaction in, 354

CH'IU, PHILIP T. Y. See LIU KUANG-YUAN, *et al.*

COHN, M. L. See CORPER, H. J., *et al.*

Control of tuberculosis among American Negroes, 332

CORPER, H. J., COHN, M. L., AND FREY, W. H. A pyridine derivative and experimental tuberculosis (Letters to the Editors), 269

CREGER, WILLIAM P. See KIRBY, WILLIAM M. M., *et al.*

Culture and tracheal lavage in pulmonary tuberculosis, 634

——, Choice and standardization of, in experimental tuberculous infection in mice, 90

CUMMINGS, MARTIN, AND HOLLOWAY, JAMES B., JR. An evaluation of a method of obtaining gastric washings, 228

——. See SPENDLOVE, GEORGE A., *et al.*

——. See FROBISHER, M., JR., *et al.*

Cytolysis, *in vitro*, of leukocytes by tuberculin, 212

DAVIS, J. DWIGHT, AND WEINBERG, JOSEPH. Pleural decortication in pulmonary tuberculosis, 288

Decortication, pleural, in pulmonary tuberculosis, 288

DESSAU, F. I., YEAGER, R. L., AND KULISH, M. A simplified guinea pig test for tuberculostatic agents, 223

DEWING, STEPHEN B., AND MORGANSTERN, PHILIP. Insulin in the treatment of tuberculous patients with anorexia, a modified technique, 25

Diet, high-protein, Urinary excretion of amino acids by normal subjects on, 439

——, ——, Urinary excretion of amino acids by tuberculous subjects on, 448

——, low-protein, Urinary excretion of amino acids by normal subjects on, 439

——, ——, Urinary excretion of amino acids by tuberculous subjects on, 448

Dihydrostreptomycin, Comparison with

streptomycin in avian tuberculosis in chicks, 366
——, Study of toxicity of, 564
DL Serine, Toxic effects of, on virulent tubercle bacilli (Letters to the Editors), 385
DOLLEY, FRANK S., AND BREWER, LYMAN A., III. Tumors of the mediastinum: A discussion of diagnostic procedure and surgical treatment based on experience with forty-four operated cases, 419
DOMON, CHARLES M., KILBOURNE, PHILLIP C., AND KING, ERNEST Q. A clinical study of the toxic effects of dihydrostreptomycin and streptomycin, 564
DONAVICK, R., AND BERNSTEIN, J. On the action of thiosemicarbazones in experimental tuberculosis in the mouse (Letters to the Editors), 539
——, AND RAKE, G. Tuberculostatic activity of aureomycin *in vitro* and *in vivo* (Letters to the Editors), 143
——, RICHARD. See RAKE, GEOFFREY, *et al.*
——, MCKEE, CLARA M., JAMBOR, WILLIAM P., AND RAKE, GEOFFREY. The use of the mouse in a standardized test for antituberculous activity of compounds of natural or synthetic origin: II. Choice of mouse strain, 109
——. See MCKEE, CLARA M., *et al.*
DOONEIEF, ALFRED S., AND PICCAGLI, RUTH W. Lung trauma at pneumothorax induction, 557
DOPPELT, HARRY B. See GOLDBERG, JACOB, *et al.*
DOUGLASS, RICHMOND, AND MCAULIFFE, WILLIAM J. Pneumoperitoneum complicated by inguinal hernia: Report of a case, 524
DUBOS, RENÉ J. Immunological aspects of BCG vaccination (editorial), 670
——. Toxic effects of DL serine on virulent tubercle bacilli (Letters to the Editors), 385
——, AND SUTER, EMMANUEL. The effect of ammonium ions and aliphatic amines on the ability of virulent mycobacteria to bind neutral red (Letters to the Editors, 384
DUNN, KATHARINE REMINGTON, GETZ, HORACE R., DUNN, MAX S., CAMIEN, MERRILL N., AKAWIE, SHIRLEY, MALIN, RUTH B., AND EIDUSON, SAMUEL. The urinary excretion of amino acids: II. By tuberculous male subjects on controlled low- and high-protein diets, 448
——. See DUNN, MAX S., *et al.*
——, MAX S., CAMIEN, MERRILL N., AKAWIE, SHIRLEY, MALIN, RUTH B., EIDUSON, SAMUEL, GETZ, HORACE R., AND DUNN, KATHARINE REMINGTON. The urinary excretion of amino acids: I. By normal male subjects on controlled low- and high-protein diets, 439
——. See DUNN, KATHARINE REMINGTON, *et al.*
DWORK, RALPH E. See JONES, WM. WILEY, *et al.*

EDITORIALS:
Cost of tuberculosis research, 527
Immunological aspects of BCG vaccination, 670
Integration of streptomycin with other forms of therapy for pulmonary tuberculosis, 264
Necessity for accurate evaluation of the results of thoracoplasty, 383
Tuberculosis in medical teaching, 140
EIDUSON, SAMUEL. See DUNN, KATHARINE REMINGTON, *et al.*
——. See DUNN, MAX S., *et al.*
Enterocolitis, obstructive tuberculous, 648
——, tuberculous, 576
Erythema induratum Bazin, 249
EVANS, JOHN A. See FELLOWS, HAYNES HAROLD, *et al.*

FAVOUR, CUTTING B., FREMONT-SMITH, PAUL, AND MILLER, JOSEPH M. Factors affecting the *in vitro* cytolysis of white blood cells by tuberculin, 212
FEIND, CARL R., AND FOWLER, EDMUND P., JR. Toxicity of streptomycin for the auditory and vestibular mechanisms, 39
FELLOWS, HAYNES HAROLD, EVANS, JOHN A., AND STEPHENS, MARGARET G. Disposition and follow-up of pulmonary tuberculosis: A study based on the initial roentgenogram, 487
FITZPATRICK, WILLIAM J., AND SCHWARTZ, STEVEN O. Polycythemia secondary to tuberculosis of the spleen, 660
Food intake of women with active tuberculosis, 455
—— —— —— —— with arrested tuberculosis, 455

Fowler, Edmund P., and Feind, Carl R. Toxicity of streptomycin for the auditory and vestibular mechanisms, 39
Fox, Theodore T., Jaffe, Henry L., and Lichenstein, Louis. Erythema nodosum Bazin. Report of proved case associated with tuberculous lymphadenitis, completely relieved by tuberculin desensitization, 249
Freedman, Benjamin. Pulmonary adenomatosis: Report of a case, 258
Fremont-Smith, Paul. See Favour, Cutting B., *et al.*
Frey, W. H. See Corper, H. J., *et al.*
Friedlander, Ralph. See Goldberg, Jacob, *et al.*
Friedman, Eli, and Silverman, Irving. The effect of antihistamine medication on the tuberculin reaction in children, 354
Frobisher, M., Jr., Klein, G. C., and Cummings, M. M. Preservation of mycobacteria by desiccation *in vacuo*, 621

Gastric washings. See Washings, gastric
Getz, Horace R. See Dunn, Katharine Remington, *et al.*
——. See Dunn, Max S., *et al.*
Goldberg, Jacob, Friedlander, Ralph, Doppelt, Harry B., and Miller, Dorothy E. Physical therapy in postthoracoplasty, 189
Golley, Paul M. Routine chest photoroentgenography in Baroness Erlanger Hospital, Chattanooga, Tennessee, 377
Granulomatosis, pulmonary, after beryllium exposure, 755
Grayzel, David M., and Zarowitz, Harold. Tuberculous arteritis of the abdominal aorta with rupture into the third portion of the duodenum (Case report), 801
Gregory, Francis J. See Solotorovsky, Morris, *et al.*
Guinea pig test for tuberculostatic agents, 223

Hamilton, W. F., and Pamplona, P. A. Miniature chest roentgenograms in schools and industries in San Antonio, Texas, 501
Hand, M. Ethel. See Smith, Mapheus, *et al.*
Head, Jerome, R., and Moen, Chester W. Late nontuberculous complications of calcified hilus lymph nodes, 1
Hemidiaphragm, paralyzed, Effect of, on results of homolateral thoracoplasty, 183
Henderson, Alfred R. The effect of antihistamine medication on the tuberculin reaction (Letters to the Editors), 811
Hemorrhage, fatal, in pulmonary tuberculosis, 589
Hemothorax, massive, complicating therapeutic pneumothorax, 654
Hernia, inguinal, complicating pneumoperitoneum, 524
Hinshaw, H. Corwin, and Olsen, Arthur M. Tuberculosis of the trachea and major bronchi: Results of treatment with streptomycin, 32
Hobby, Gladys L., Regna, Peter P., and Lenert, Tulita F. The chemotherapeutic action of streptomycin paraaminosalicylate in experimental tuberculosis in mice (Letters to the Editors), 808
Holden, H. M. A case of massive hemothorax complicating therapeutic pneumothorax, 654
Holloway, James B., Jr., and Cummings Martin. An evaluation of a method of obtaining gastric washings, 228
Howard, W. L. See Yanitelli, S. A., *et al.*
Hutchison, Dorris. See Waksman, Selman, A., *et al.*
Hypertension, terminal, sarcoidosis with, 236

Ileostomy "nonsurgical" for tuberculous enterocolitis, 648
Industries, miniature roentgenograms in, 501
Infarction, pulmonary, Location of, 206
Infection in mice, Experimental tuberculous, 90, 109, 121
Insulin treatment of tuberculous patients with anorexia, 25
In vitro cytolysis of leukocytes by tuberculin, 212
Ions, ammonium, Effect of, on ability of virulent mycobacteria to bind neutral red (Letters to the Editors), 384

Jackson, E. L. See Smith, M. I., *et al.*
Jacox, Ralph F., and Meade, Gordon M. Variation induration of tuberculin skin

sensitivity produced by two strains of BCG, 541
JAFFE, HENRY L. See FOX, THEODORE T., *et al.*
JAMBOR, WILLIAM P. See RAKE, GEOFFREY, *et al.*
——. DONOVICK, RICHARD, *et al.*
——. See McKEE, CLARA M., *et al.*
JOLLY, PAUL N., AND PLESSINGER, VIRGIL A. Rasmussen's aneurysms and fatal hemorrhage in pulmonary tuberculosis, 589
JONES, OSWALD, R., PLATT, WARREN D., AND AMILL, LUIS A. Miliary tuberculosis caused by intravenous self-injection of tubercle bacilli, treated successfully with streptomycin therapy, 514
——, WM. WILEY, NELSON, CLARENCE, DWORK, RALPH E. Repeated transcutaneous autolytic tuberculin tests in children, 45
JUNGE, J. M. See SMITH, M. I., *et al.*

KATZ, EDWARD. See WAKSMAN, SELMAN A., *et al.*
KENT, EDWARD M. The surgical importance of the anatomical distribution of the pulmonary segments, 699
KILBOURNE, PHILLIP C. See DOMON, CHARLES M., *et al.*
KING, DONALD S. Roentgenograms of diffuse pulmonary lesions (Letters to the Editors), 536
——, ERNEST, Q. See DOMON, CHARLES M., *et al.*
KIRBY, WILLIAM M. M., SIMPSON, ROBERT M., AND CREGER, WILLIAM P. Streptomycin therapy of tuberculous pneumonia in Negro adults, 343
KLEIN, G. C. See FROBISHER, M., JR., *et al.*
KLOPSTOCK, ROBERT, AND RUBIN, MORRIS. Influence of type of disease on the results of thoracoplasty in pulmonary tuberculosis, 273
KU, HSIEN-CHIH. See LIU, KUANG-YUAN, *et al.*
KULISH, M. See DESSAU, F. I., *et al.*

LAUBACH, C. A., JR., AND VIVAS, J. R. Observations on lower lobe disease in pulmonary tuberculosis, 15
Lavage, tracheal, and culture in pulmonary tuberculosis, 634
LENERT, TULITA F. See HOBBY, GLADYS L., *et al.*
Leprosy, murine, Chemotherapy of, 359
Lesion, sarcoid-like, in guinea pigs, 236
Lesions, diffuse pulmonary, Roentgenograms of (Letters to the Editors), 536
LETTERS TO THE EDITORS:
Chemotherapeutic action of streptomycin para-aminosalicylate in experimental tuberculosis in mice, 808
Effect of ammonium ions and aliphatic amines on ability of virulent mycobacteria to bind neutral red, 384
Effect of antihistamine medication on tuberculin reaction, 811
Intravenous administration of p-aminosalicylic acid, 385
On the action of thiosemicarbazones in experimental tuberculosis in the mouse, 539
Pyridine derivative and experimental tuberculosis, 269
Roentgenograms of diffuse pulmonary lesions, 536
Toxic effects of DL serine on virulent tubercle bacilli, 385
Tuberculostatic activity of aureomycin *in vitro* and *in vivo*, 143
What's wrong with mass X-ray surveys? 532
Leukocytes, *in vitro* cytolysis of, by tuberculin, 212
Lichtenstein, Louis. See FOX, THEODORE T., *et al.*
——, M. R. See SWEANY, HENRY C., *et al.*
LIU, KUANG-YUAN, KU, HSIEN-CHIH, AND CH'IU, PHILIP T. Y. The suitable dose of tuberculin for single test tuberculin testing, 483
Lobe disease, lower, Observations on, in pulmonary tuberculosis, 15
LOWRY, HOPE, AND BERRY, J. W. A slide culture method for the early detection and observation of growth of the tubercle bacillus, 51
Lung, Resected postthoracoplasty, 406
—— trauma at pneumothorax induction, 557
Lymph nodes, calcified. See Lymph nodes, hilus
—— ——, hilus, calcified, Late nontuberculous complications of, 1
Lymphadenitis, tuberculous, associated with erythema induratum, 249

MALIN, RUTH B. See DUNN, KATHARINE REMINGTON, *et al.*

Malin, Ruth B. See Dunn, Max S., *et al.*
McAuliffe, William J., and Douglass, Richmond. Pneumoperitoneum complicated by inguinal hernia: Report of a case, 524
McKee, Clara M. See Rake, Geoffrey, *et al.*
——. See Donowick, Richard, *et al.*
——, Rake, Geoffrey, Donowick, Richard, and Jambor, William P. The use of the mouse in a standardized test for antituberculous activity of compounds of natural or synthetic origin: I. Choice and standardization of culture, 90
Meade, Gordon M., and Jacox, Ralph F. Variation in duration of tuberculin skin sensitivity produced by two strains of BCG, 541
——, Richard, H., Jr., and Blades, Brian B. The surgical treatment of recurrent and chronic spontaneous pneumothorax of nontuberculous origin, 683
Medisatinum, Tumors of, 419
Meissner, William A., Overholt, Richard H., Wilson, Norman J., and Walker, James A. The resected post-thoracoplasty lung. A clinico-pathologic correlation, 406
Method, Evaluation of, of obtaining gastric washings, 228
Mice, Experimental tuberculosis in (Letters to the Editors), 808
——, —— tuberculous infection in, 90, 109, 121
Miller, Dorothy E. See Goldberg, Jacob, *et al.*
——, Joseph M. See Favour, Cutting, B., *et al.*
Mitchell, Roger S. Phrenic nerve interruption in the treatment of pulmonary tuberculosis: II. Complications and sequelae of phreniclasis, 168
——. Phrenic nerve interruption in the treatment of pulmonary tuberculosis: III. Effect of a paralyzed hemi-diaphragm on the results of homolateral thoracoplasty, 183
Moen, Chester, W. and Head, Jerome R. Late nontuberculous complications of calcified hilus lymph nodes, 1
Morgenstern, Philip, and Dewing, Stephen B. Insulin in the treatment of tuberculous patients with anorexia—a modified technique, 25
Mouse, Action of thiosemicarbazones in experimental tuberculosis in (Letters to the Editors), 539
—— strain, Choice of, in experimental tuberculous infection in mice, 109
Mueller, E. E. See Yanitelli, S. A., *et al.*
Muschenheim, Carl. Tuberculosis in medical teaching (editorial), 140
Mycobacteria, Neomycin activity on, 78
——, Preservation of, by desiccation *in vacuo*, 621
M. tuberculosis, Neomycin activity on, 78
——, Slide cultures for detection of, 51

Negro adults, Streptomycin therapy of tuberculous pneumonia in, 343
Negroes, American, Tuberculosis control among, 332
Nelson, Clarence. See Jones, Wm. Wiley, *et al.*
Neomycin activity on *Mycobacterium tuberculosis* and other mycobacteria, 78
Neurotoxicity of streptomycin, 39
Nurses, Tuberculosis in, 305

Obituaries:
George Chambers Anglin, 1890–1948, 388
Bruce H. Douglas, 1892–1949, 812
Strachimer A. Petroff, 1883–1948, 387
O'Connor, John B. Integration of streptomycin with other forms of therapy for pulmonary tuberculosis (editorial), 264
Ohlson, Margaret A. See Brewer, Wilma D., *et al.*
Olsen, Arthur M., and Hinshaw, H. Corwin. Tuberculosis of the Trachea and major bronchi: Results of treatment with streptomycin, 32
Overholt, Richard H. See Meissner, William A., *et al.*

Pamplona, P. A., and Hamilton, W. F. Miniature chest roentgenograms in schools and industries in San Antonio, Texas, 501
Panarteritis, sarcoidosis with, 236
Pansy, Felix. See Rake, Geoffrey, *et al.*
P-aminosalicylic acid, Intravenous administration of (Letters to the Editors), 385
Patnode, Robert A. See Spendlove, George A., *et al.*
Payne, Howard M. The problem of tuberculosis control among American Negroes, 332

Periarteritis, sarcoidosis with, 236
Pharmacologic studies of new sulfones and streptomycin in experimental tuberculosis, 62
PHILLIPS, SAMUEL, AND WOODBURY, JOHN W. Treatment of acute obstructive tuberculous enterocolitis by "nonsurgical ileostomy" and streptomycin. A case report, 648
Photo-roentgenography, routine chest, 377
Phrenic nerve interruption in the treatment of pulmonary tuberculisis, 168, 183
Phreniclasis, Complications and sequelae of, 168
PICCAGLI, RUTH W., AND DOONEIEF, ALFRED S. Lung trauma at pneumothorax induction, 557
PLACE, RONALD. See WRIGHT, GEORGE W., *et al.*
PLATT, WARREN D. See JONES, OSWALD R., *et al.*
PLESSINGER, VIRGIL A., AND JOLLY, PAUL N. Rasmussen's aneurysms and fatal hemorrhage in pulmonary tuberculosis, 589
Pneumocele, abdominal, following artificial pneumoperitoneum, 520
Pneumonia, tuberculous, in Negro adults, Streptomycin therapy of, 343
Pneumoperitoneum, artificial, followed by abdominal pneumocele, 520
—— complicated by inguinal hernia, 524
——, Diaphragmatic rupture during, 794
——, Physiological effects of, upon respiratory apparatus, 706
Pneumothorax, chronic, 683
—— induction, Lung trauma at, 557
—— of nontuberculous origin, 683
——, recurrent, 683
—— resulting from diaphragmatic rupture, 794
——, spontaneous, Surgical treatment of, 683
——, therapeutic, complicated by massive hemothorax, 654
Postthoracoplasty, Physical therapy in, 189
POTTENGER, F. M. Auscultation, 639
PRINCI, FRANK. See WRIGHT, GEORGE W., *et al.*
Pulmonary infarction. See Infarction, pulmonary
—— segments. See segments, pulmonary
—— tuberculosis. See Tuberculosis, pulmonary
Pyridine derivative and experimental tuberculosis (Letters to the Editors), 269

Radiography, mass, Appraisal of, in discovery of pulmonary tuberculosis, 466
Radio tube manufacture, Exposure to beryllium in, 755
RAKE, G., AND DONOVICK, R. Tuberculostatic activity of aureomycin *in vitro* and *in vivo* (Letters to the Editors), 143
——. See DONOVICK, RICHARD, *et al.*
——, JAMBOR, WILLIAM P., MCKEE, CLARA M., PANSY, FELIX, WISELOGLE, FREDERICK Y., AND DONOVICK, RICHARD. The use of the mouse in a standardized test for antituberculous activity of compounds of natural or synthetic origin: III. The standardized test, 121
——. See MCKEE, CLARA M., *et al.*
Rasmussen's aneurysms in pulmonary tuberculosis, 589
REGNA, PETER P. See HOBBY, GLADYS L., *et al.*
Research in tuberculosis, Cost of (editorial), 527
—— on tuberculosis in the United States, Cost of, 393
Resection. See Lung, resected postthoracoplasty
REYNOLDS, LESTER T. See SMITH, MAPHEUS, *et al.*
ROBERTS, E. GWYN. See WARDRIP, BUFORD H., *et al.*
Roentgenograms, miniature, in schools and industries in San Antonio, Texas, 501
—— of diffuse pulmonary lesions (Letters to the Editors), 536
ROSENTHAL, SOL ROY. Pathological and experimental studies of Boeck's sarcoid. 1. Report of a case with panarteritis, periarteritis, terminal-hypertension and uremia, and the reproduction of a sarcoid-like lesion in guinea pigs, 236
RUBIN, MORRIS, AND KLOPSTOCK, ROBERT. Influence of type of disease on the results of thoracoplasty in pulmonary tuberculosis, 273
Rupture, diaphragmatic, during pneumoperitoneum, 794
Sarcoidosis with panarteritis, 236
—— —— periarteritis, 236
—— —— reproduction of a sarcoid-like lesion in guinea pigs, 236
—— —— terminal-hypertension, 236
—— —— uremia, 236

Scarborough, C. Gerald. See Wardrip, Buford H., *et al.*
Segments, pulmonary, surgical importance of anatomical distribution of, 699
Selective Service registrants, Tuberculosis among, 773
Schools, miniature roentgenograms in, 501
Schwartz, Steven O., and Fitzpatrick, William J. Polycythemia secondary to tuberculosis of the spleen, 660
Sensitivity, Tuberculin skin, variation in duration of, after BCG, 541
Shipman, Sidney J., Stephens, H. Brodie, and Binkley, Frederick M. Pulmonary alveolar adenomatosis (Case report), 788
Siegel, Henry. See Solotorovsky, Morris, *et al.*
Silverman, Charlotte. An appraisal of the contribution of mass radiography in the discovery of pulmonary tuberculosis, 466
——, Irving, and Friedman, Eli. The effect of antihistamine medication on the tuberculin reaction in children, 354
Simpson, Robert M. See Kirby, William M. M., *et al.*
Slavin, Paul. Diffuse pulmonary granulomatosis in young women following exposure to beryllium compounds in the manufacture of radio tubes, 755
Slide cultures for detection of *M. tuberculosis*, 51
Smith, Mapheus, Reynolds, Lester T., and Hand, M. Ethel. Tuberculosis among Selective Service registrants, 773
—— M. I., Jackson, E. L., Junge, J. M., and Bhattacharya, B. K. The pharmacologic and chemotherapeutic action of some new sulfones and streptomycin in experimental tuberculosis, 62
Solotorovsky, Morris, Siegel, Henry, Bugie, Elizabeth, J. and Gregory, Francis J. The evaluation of antituberculous agents with avian tuberculosis in chicks: A comparison of dihydrostreptomycin and streptomycin, 366
Spendlove, George A., Cummings, Martin M., and Patnode, Robert A. Toxicity of sputum digestants to tubercle bacilli in water and sputum, 628
Spleen, Tuberculosis of, 660
Sputum digestants, Toxicity of, for tubercle bacilli, 628
Steele, John D. The necessity for the accurate evaluation of the results of thoracoplasty (editorial), 383
Stephens, H. Brodie. See Shipman Sidney J., *et al.*
——, Margaret G. See Fellows, Haynes, Harold, *et al.*
Stokinger, Herbert. See Carpenter, Charles M., *et al.*
Streptomycin, Comparison with dihydrostreptomicin in avian tuberculosis in chicks, 366
——, integrated with other forms of therapy for pulmonary tuberculosis (editorial), 264
—— in intestinal tuberculosis, 576
—— para-aminosalicylate in experimental tuberculosis in mice (Letters to the Editors), 808
——, Pharmacologic studies of, in experimental tuberculosis, 62
——, neurotoxicity of, 39
—— regimens, Evaluation of, in treatment of tuberculosis, 715
——, study of toxicity of, 564
—— therapy of tuberculous pneumonia in Negro adults, 343
——, Toxicity of, for auditory and vestibular mechanisms, 39
—— treatment of tuberculous enterocolitis, 576
—— for tuberculous enterocolitis, 648
—— in tracheobronchial tuberculosis, 32
—— —— treatment of miliary tuberculosis, 514
Stringer, C. J. See Brewer, Wilma D., *et al.*
Suhrland, Leif G. See Carpenter, Charles M., *et al.*
Sulfones, new, Pharmacologic studies of, in experimental tuberculosis, 62
Suter, Emmanuel, and Dubos, René J. The effect of ammonium ions and aliphatic amines on the ability of virulent mycobacteria to bind neutral red (Letters to the Editors), 384
Sweany, Henry C., Lichenstein, M. R., Turner, George C., and Berard LeRoy. Streptomycin treatment of tuberculous enterocolitis, 576

Test, guinea pig, for tuberculostatic agents, 223
Tests in children, Transcutaneous autolytic tuberculin, 45

Tests in children, simple, of ventilatory function, 149
Therapy, physical, in postthoracoplasty, 189
Thiosemicarbazones, Action of, in experimental tuberculosis in mouse (Letters to the Editors), 539
Thoracoplasty. See Lung, Resected post-thoracoplasty.
——, homolateral, Effect of paralyzed hemidiaphragm on, 183
—— results in pulmonary tuberculosis, Influence of type of disease on, 273
—— ——, necessity for accurate evaluation of (editorial), 383
Toxicity of dihydrostreptomycin and streptomycin, 564
—— —— sputum digestants for tubercle bacilli, 628
—— —— streptomycin for auditory and vestibular mechanisms, 39
Trachea, Tuberculosis of, 604
——, —— ——, Streptomycin in treatment of, 32
Transcutaneous autolytic tuberculin tests in children, 45
Trauma, lung, at pneumothorax induction, 557
Tubercle bacilli. See Bacilli, tubercle
Tuberculin desensitization, relieving case of erythema nodosum, 249
——, Dose of, for single test, 483
——, *in vitro* cytolysis of leukocytes by, 212
—— reaction in children, Effect of antihistamine medication on, 354
—— ——, Effect of antihistamine medication (Letters to the Editors), 811
—— skin sensitivity, Variation in duration of, after BCG, 541
——, transcutaneous autolytic tests in children, 45
Tuberculosis, active, Food intake of women with, 455
——, among Selective Service registrants, 773
——, arrested, Food intake of women with, 455
Tuberculosis, avian, in chicks, 366
—— control among American Negroes, 332
——, Cost of research in (editorial), 527
——, Evaluation of streptomycin regimens in treatment of, 715
——, experimental, in mouse, Action of thiosemicarbazones in (Letters to the Editors), 539
Tuberculosis, experimental, Pharmacologic and chemotherapeutic studies of new sulfones and streptomycin in, 62
—— in medical teaching (editorial), 140
—— —— Nurses, 305
——, intestinal, Streptomycin in, 576
—— —— United States, Cost of research on, 393
——, miliary, treated with streptomycin, 514
——, pulmonary, Appraisal of mass radiography in discovery of, 466
——, ——, Disposition and follow-up of, 487
——, ——, Fatal hemorrhage in, 589
——, ——, Integration of streptomycin with other forms of therapy for (editorial), 264
——, ——, Observations on lower lobe disease in, 15
——, ——, Phrenic nerve interruption in treatment of, 168, 183
——, ——, Pleural decortication in, 288
——, ——, Results of thoracoplasty in, 273
——, ——, Tracheal lavage and culture in, 634
—— of spleen, 660
—— resistance in guinea pigs subsequent to BCG vaccination, 547
——, tracheobronchial, 604
——, ——, Streptomycin in treatment of, 32
Tucker, William B. Evaluation of streptomycin regimens in treatment of tuberculosis, 715
Tumors of mediastinum, 419
Turner, George C. See Sweany, Henry C., *et al.*

Uremia, sarcoidosis with, 236

Ventilatory function, simple tests of, 149
Vivas, J. R., and Laubach, C. A., Jr. Observations on lower lobe disease in pulmonary tuberculosis, 15
Wadley, F. M. The use of biometric methods in comparison of acid-fast allergens, 131
Walker, James H. See Meissner, William A., *et al.*
Waksman, Selman A., Hutchison, Dorris, and Katz, Edward. Neomycin activity upon *Mycobacterium tuberculosis* and other mycobacteria, 78
Wardrip, Buford H., Scarborough, C. Gerald, and Roberts, E. Gwyn. The

combined use of tracheal lavage and culture as a diagnostic procedure in pulmonary tuberculosis, 634

WARRING, FREDERICK C., JR. Simple tests of ventilatory function for use in the sanatorium or clinic, 149

Washings, gastric, Evaluation of method of obtaining, 228

WEINBERG, JOSEPH, AND DAVIS, J. DWIGHT. Pleural decortication in pulmonary tuberculosis, 288

WILSON, NORMAN J. See MEISSNER, WILLIAM A., *et al.*

WISELOGLE, FREDERICK Y. See RAKE, GEOFFREY, *et al.*

WOODBURY, JOHN W., AND PHILLIPS, SAMUEL. Treatment of acute obstructive tuberculous enterocolitis by "nonsurgical ileostomy" and streptomycin. A case report, 648

WOODRUFF, C. E. See YANNITELLI, S. A., *et. al.*

WORTMAN, H. C., AND BASS, H. E. Abdominal pneumocele following artificial pneumoperitoneum, 520

WRIGHT, GEORGE W., PLACE, RONALD, AND PRINCI, FRANK. The physiologic effects of pneumoperitoneum upon the respiratory apparatus, 706

X-Ray surveys, What's wrong with (Letters to the Editors), 532

YANNITELLI, S. A., WOODRUFF, C. E., MUELLER, E. E., AND HOWARD, W. L. Fatal tension pneumothorax resulting from diaphragmatic rupture in a patient receiving pneumoperitoneum (case report), 794

YEAGER, R. L. See DESSAU, F. I., *et al.*

ZAROWITZ, HAROLD, AND GRAYZEL, DAVID M. Tuberculous arteritis of the abdominal aorta with rupture into the third portion of the duodenum (case report), 801

ZINS, EUGENE I. Concerning the location of pulmonary infarction, 206

LIST OF JOURNALS FROM WHICH ARTICLES WERE ABSTRACTED FOR INCLUSION IN VOLUME 60

Acta tuberculosea Belgica
Acta tuberculosea Scandinavica
American Heart Journal
American Journal of Clinical Pathology
American Journal of Diseases of Children
American Journal of the Medical Sciences
American Journal of Pathology
American Journal of Physiology
American Journal of Public Health and the Nation's Health
American Journal of Roentgenology and Radium Therapy
Annales de l'Institut Pasteur
Annals of Allergy
Annals of Internal Medicine
Annals of Surgery
Archives of Internal Medicine
Archives of Pathology

British Journal of Radiology
British Medical Journal

Chinese Medical Journal

Diseases of the Chest

Hoja tisiológica

Industrial Medicine including Industrial Hygiene Section

Journal of the American Medical Association
Journal of the American Veterinary Medical Association
Journal of Biological Chemistry
Journal of Experimental Medicine
Journal of Laboratory and Clinical Medicine
Journal of the National Medical Association
Journal of Pediatrics

Lancet
Lekarske listy

Medical Clinics of North America

New England Journal of Medicine

Poumon
Presse médicale
Problemy tuberkuleza
Proceedings of the Society for Experimental Biology and Medicine
Public Health Reports

Quarterly Bulletin of Sea View Hospital
Quarterly Journal of Medicine

Radiology
Revista de tuberculosis del Uruguay
Revista mexicana de tuberculosis y infermedades de aparato respiratorio
Revue de la tuberculose
Rozhledy v Tuberculose

Schweizerische medizinische Wochenschrift
Schweizerische Zeitschrift für Tuberculose
Science
Semaine des Hôpitaux
Surgery, Gynecology and Obstetrics with International Abstract of Surgery

Tegen de Tuberculose
Thorax
Tubercle

Wiener klinische Wochenschrift

INDEX OF ABSTRACTS

Clinical Studies, Tuberculosis
1-2, 17-20, 33-35, 49-51, 65-67

Clinical Studies, Nontuberculous Diseases
2-6, 20-26, 35-42, 51-58, 67-70

Antimicrobial Therapy
6-8, 26-28, 42-45, 59-61, 70-73

Laboratory Studies
8-15, 28-31, 45-47, 61-62, 74-78

Public Health and Epidemiology
15-16, 31-32, 47-48, 62-64, 78-80

Abscess, lung, acute, 24
——, ——, putrid, 24
——, tuberculous, following penicillin injection, 35
Acid, para-aminosalicylic, 26
——, ——, for tuberculosis, 26
Actinomycosis, pulmonary, 41
Adams, J. M. Primary pneumonitis, 22
Addison's disease with tuberculosis, 44
Adenoma, bronchial, 5
Adenomatosis, pulmonary, 25
Adults, BCG in, 31
Air-borne bacteria. See Bacteria, air-borne
Alin, K., and Helander, S. Tissue distribution of PAS, 30
Altitude and artificial respiration, 77
Altschule, M. D., and Lewis, H. D. Carbonic anhydrase in blood, 78
Amebiasis, Thoracic complications of, 52
Amyloidosis, Insulin tolerance in, 30
Andrews, G. W. S., Pickering, G. W., and Sellors, T. H. Constrictive pericarditis, 18
Anemia, hemolytic, Pneumonia in, 37
Aneurysms, myotic pulmonary arterial, 54
Angiocardiography of great vessels, 58
Antihistaminic drugs with streptomycin, 27
Anttila, S. Early intrapleural pneumonolysis, 19
ANTU, cause of pulmonary edema, 75
Aronoff, J. S. See Gilbert, J. G., *et al.*
Aronson, A., and Dwight, R. W. Streptomycin for tuberculous endometritis, 43
Arteries, bronchial, in bronchiectasis, 61
Artery, pulmonary, Respiration after ligation of, 76
Artificial respiration and altitude, 77
Asphyxia, obstructive, Resuscitation from, 76
Aspiration biopsy of lung lesions, 56
Asthma, bronchial, fluids for, 38
——, tropical eosinophilic, 38
Atelectasis, experimental, pulmonary, 77
——, linear, 53
Atkins, J. P. See Hodes, P. J. *et al.*
Atmospheric pollution, industrial, 32
Atypical pneumonia. See Pneumonia, atypical
Aureomycin for atypical pneumonia, 28
—— —— primary atypical pneumonia, 73
—— —— tularemia, 73
Azzopardi, P. G., and Fridjohn, L. Spontaneous mediastinal emphysema, 69

Bacillary wax and delayed hypersensitivity, 29
Bacilli, tubercle, Culture of, 75
——, ——, Effect of chick embryo extract on, 9
——, ——, fluorescent microscopy of, 62
——, ——, sphingomyelin and growth of, 10
——, ——, streptomycin resistance of, 72
——, ——, -resistant, 44
——, ——, wetting agents and growth of, 10
——, vole tubercle, Reaction to, 78
——, ——, vaccination with, 78
Bacteria, air-borne, and humidity, 12
Basal tuberculosis. See tuberculosis, basal
Bass, H. E. Pneumonitis following bronchography, 40
——, Schomer, A., and Berke, R. Coccidioidomycosis, 42
Bastide, J., de Casanova, J. Arrighi, Roussel, P., Monfajon, Ch. Alberet. Streptomycin for bone and joint tuberculosis, 71
Battro, A., Bidoggia, H., Pietrafesa, E., and Labourt, F. E. Blood pressure and respiration, 14
Bauxite-fume pneumoconiosis, 67

BCG in adults, 31
—— for students, 63
—— usage in Chicago, 63
—— vaccination, Complications of, 20
——, virulence variations of, 29
Beck, M., Bell, J., Shaw, E., and Huebner, R. Q Fever, 32
Beham, H., and Perr, H. Streptomycin stomatitis, 8
Belcher, J. R. Pulmonary complications of dysphagia, 39
Belgian Congo, Tuberculosis in, 78
Bell, J. See Beck, M., *et al.*
Benioff, M. A. See Farber, S. M., *et al.*
Benzoic acid oxidation, Kinetics of, 61
Berard, M. See Galy, P., *et al.*
Bergman, M., Shatz, B. A., and Flance, I. J. Tumor cells in sputum, 5
Berke, R. See Bass, H. E., *et al.*
Bérnard, E., Lotte, A., Weill, J., Monod, R., Mathey and Monod, Streptomycin and surgery, 72
——, Padavani, P., and Lotte, A. Streptomycin for bone and joint tuberculosis, 71
Bernheim, F. See Eadie, G. S., *et al.*
Bernou, A., Goyer, L., Marceaux, & Tricoire, J. Cavernostomy, 66
Bertheau. See LeFoyer, *et al.*
Beryllium pneumonitis, 51
Bevilacqua, E. B., and McCarter, J. R. Tuberculoproteins, 11
Bidoggia, H. See Battro, A., *et al.*
Bignall, J. R., and Crofton, J. Antihistaminic drugs with streptomycin, 27
Biopsy, aspiration, of lung lesions, 56
Bjørnstad, R. Th. Tuberculosis and sarcoidosis, 20
Black, R. A. BCG usage in Chicago, 63
Blades, B. Empyema, 28
Blanch, H. Cantonnet. See Blanch, P. Cantonnet, *et al.*
——, P. Cantonnet, Blanch, H. Cantonnet, and Scremini, A. Pérez. Complications of BCG vaccination, 20
Blattberg, B., and Ehrhorn, H. Streptomycin resistance of tubercle bacilli, 72
Bloch, Hubert. Effect of chick embryo extract on tubercle bacilli, 9
——, R. Tuberculous calcification, 51
Blood, Carbonic anhydrase in, 78
Blood, F. R., and D'Amour, F. E. Artificial respiration and altitude, 78
Blood pressure and respiration, 14
Bloomer, W. E., Harrison, W., Lindskog, G. E., and Liebow, A. A. Respiration after pulmonary artery ligation, 76
Bobrowitz, I. D., and Hurst, A. Minimal tuberculosis, 50
Bøe, J. Virulence variations of BCG, 29
Boeck's sarcoid, 2
Boisvert, H. See Bretey, J., *et al.*
Bone and joint tuberculosis. See tuberculosis of bone and joint.
Bretey, J., Coletsos, P. J., and Boisvert, H. Test of streptomycin sensitivity, 74
Breton, A. See Gernez-Rieux, Ch., *et al.*
Bronchi in primary childhood tuberculosis, 33
Bronchial asthma, fluids for, 38
—— washings. See Washings, bronchial
Bronchiectasis, Bronchial arteries in, 61
——, Histopathology of, 23
——, Surgical treatment of, 69
Bronchitis, chronic, 38
——, circumscribed, 67
Bronchogenic carcinoma, 36
Bronchography followed by pneumonitis, 40
Bronchoscopy and primary complex, 17
Bruins, A.E.G. de Vries. Overcrowding and tuberculous mortality, 62
Bryer, M. S., and Schoenbach, E. B. Aureomycin for atypical pneumonia, 28
Bullous emphysema. See Emphysema, bullous
Bunnell, I. See Furculow, M., *et al.*
——, and Furcolow, M. Histoplasmosis, 21
Burkhardt, W. L. See Schwerma, H., *et al.*
Burnett, W. E. See Rosemond, G. P., *et al.*

Calciferol for skin tuberculosis, 66
Calcification, tuberculous, 51
Campbell, G. S., and Visscher, M. B. Pulmonary edema and intracranial pressure, 76
——, H. W. See Cochrane, A. L., *et al.*
Cancer, lung, Cytologic diagnosis of, 55
Capillary pressure, pulmonary, 14
Cara, M., and Scheiner, Z. Experimental pulmonary atelectasis, 77
Carbonic anhydrase in blood, 78
Carcinoma, bronchogenic, 36, 69
——, of lung, 55
——, sputum smears for, 36
Cardiac failure and scoliosis, 37
Casal, J. M. Acute lung abscess, 24
Cathie, I. A. B. Streptomycin and streptokinase for tuberculous meningitis, 42

Cattle, coccidioidomycosis of, 42
Cavernostomy, 66
Chapman, D. W., Gugle, L. J., and Wheeler, P. W. Pulmonary infarction, 76
Cheney, M. C. Tuberculosis with Addison's disease, 44
Chest wall tuberculosis, 35
Chiari, H. Changes in meningitis after streptomycin, 6
Chicago, BCG usage in, 63
Chick embryo extract, Effect of, on tubercle bacilli, 9
Chien, Y. P. See Pan, S. C., *et al.*
Chih, C. S. See Pan, S. C., *et al.*
Childhood, Bronchi in primary tuberculosis in, 33
Children, Therapy of meningitis in, 7
——, Tuberculosis in, 49
Christie, A. C. Mass surveys, 63
Clotting time and streptomycin, 59
Coccidioidomycosis, 42
—— and tuberculosis, 66
—— of cattle, 42
Cochrane, A. L., Campbell, H. W., and Stein, S. C. Prognosis of minimal tuberculosis, 50
Cohen, R. C. Rib fracture from coughing, 66
Coletsos, P. J. See Bretey, J., *et al.*
Collapse therapy, follow-up of, 50
Colson, G. M., and Willcox, A. Bronchogenic carcinoma, 69
Complement fixation in psittacosis, 12
Complex, primary, and bronchoscopy, 17
Control, contact, during vaccination, 32
Cordy, D. R. Interstitial pneumonia in, 42
Cornbleet, T. Lupus vulgaris, 26
Cough fracture of ribs, 66
Courcoux, A. BCG in adults, 31
Crandell, W. B. See Grant, A. R., *et al.*
Crofton, J., and Bignall, J. R. Antihistaminic drugs with streptomycin, 27
——, and Mitchison, D. A. Streptomycin resistance, 6
Crouch, W. H. See Mason, E. E., *et al.*
Crusius, M. E. See Schwartzman, J., *et al.*
Cultures in Dubos medium, 8
Cummings, M. M. Laboratory diagnosis of tuberculosis, 9
——. See Spendlove, G., *et al.*
Curtis, A. C., and Grekin, R. H. Sarcoidosis, 22
Cuttino, J. T., and McCable, A. M. Granulomatous nocardiosis, 41
Cytologic diagnosis of lung cancer, 55
Cytological examination of sputum, 25
Cytolysis, tuberculin, Leukocyte blockade of, 75

Damade, P., Piéchaud, F., Traissac, F. J., Fréour, P., and Roux, M. Streptomycin for enteric tuberculosis, 71
D'Amour, F. E. Artificial respiration and altitude, 78
Darling, D. See Metcoff, J., *et al.*
Davis, D. J. Complement fixation in psittacosis, 12
——, E. W. See Judge, D. J., *et al.*
De Casanova, J. Arrighi. See Bastide, J., *et al.*
Decortication and lobectomy, 2
Deficiency in Vitamin B with streptomycin, 27
De Léobardy, J., and Lemoine, J. M. Circumscribed bronchitis, 67
Despierres, G., and Levrat, M. Paradoxical mediastinal swing in pleurisy, 2
Detloff, H. See Serée, B., *et al.*
Dexter, L. See Hellems, H. K., *et al.*
Diagnosis, cytologic, of lung cancer, 55
——, laboratory, of tuberculosis, 9
Disphagia, Pulmonary complications of, 39
Distribution in tissue of PAS, 30
Dogs, Interstitial pneumonia in, 42
Dotter, C. T., and Steinberg, I. Angiocardiography of great vessels, 58
Drinker, C. K., and Hardenburgh, E. Pulmonary edema due to ANTU, 75
Droplet, tuberculous, infection in rabbits, 11
Drugs, antihistaminic, with streptomycin, 27
Drymalski, G. W., Thompson, J. R., and Sweany, H. C. Pulmonary adenomatosis, 25
Dubos medium, Cultures in, 8
—— —— for streptomycin sensitivity, 61
——, R. J. Sphingomyelin and growth of tubercle bacilli, 10
——, and Middlebrook, G. Wetting agents and growth of tubercle bacilli, 10
Dufourt, A., and Mounier-Kuhn, P. Primary complex and bronchoscopy, 17
Dumarest, J. See Galy, P., *et al.*
Dunklin, E. W., and Puck, T. T. Humidity and air-borne bacteria, 12
Dutra, F. R. Beryllium pneumonitis, 51
Dwight, R. W., and Aronson, A. Streptomycin for tuberculous endometritis, 43
Dysgerminoma, 56

Eadie, G. S., Bernheim, F., and Fitzgerald, R. J. Kinetics of benzoic acid oxidation, 61
Edema, pulmonary, and intracranial pressure, 76

Edema, pulmonary, due to ANTU, 75
——, ——, —— to epinephrine, 13
Effusion, pleural, 17
——, tuberculous, 17
Ehrhorn, H., and Blattberg, B. Streptomycin resistance of tubercle bacilli, 72
Ehrstrom, M. Ch. Bullous emphysema with infection, 23
Elkeles, A. Pulmonary edema due to epinephrine, 13
Elson, L. Streptomycin and clotting time, 59
Embolism, pulmonary, 22, 54
Empyema, 28
——, tuberculous, 35
Emphysema, bullous, with infection, 23
——, pulmonary, 23
——, spontaneous mediastinal, 69
Endobronchial tuberculosis. See Tuberculosis, endobronchial
Endometritis, tuberculous, Streptomycin for, 43
Endothelium of the pleura, 25
Engel, M. See Furcolow, M., *et al.*
Enteric tuberculosis. See Tuberculosis, enteric.
Enteritis, tuberculous, Streptomycin for, 43, 59
Eosinophilic asthma, tropical, 38
—— granuloma of rib, 37
Eosinophilosis, pulmonary, 20
Epinephrine, Pulmonary edema due to, 13
Eppes, W. See Woodward, T. E., *et al.*
Erythema nodosum, 53
Ewart, F. E., Jr. See Pirani, C. L., *et al.*
Examination, cytological, of sputum, 25
Extrafascial pneumothorax. See Pneumothorax extrafascial
Extrapulmonary tuberculosis. See Tuberculosis, extrapulmonary

Fackler, W. See Spendlove, G., *et al.*
Fainsinger, N. H., and Oosthuizen, S. F. Pulmonary actinomycosis, 41
Fanconi, G. Therapy of meningitis in children, 7
Farber, S. M., Benioff, M. A., and McGrath, A. K. Cytologic diagnosis of lung cancer, 55
Favour, C. B. Leukocyte blockade of tuberculin cytolysis, 75
Feigin, I., and Rosenthal, J. Boeck's sarcoid, 2
Fibrosis, idiopathic, 40
—— of Lungs, interstitial, 40
——, pulmonary, 40
Finn, J. F., Jr., Weller, Th., and Morgan, H. R. Epidemic pleurodynia, 38
Firket, J. Tuberculosis in Belgian Congo, 78
Fitzgerald, R. J. See Eadie, G. S., *et al.*
Flance, I. J. See Bergman, M., *et al.*
Fluorescent method. See method, fluorescent
Fond, I. and Ravenna, P. Tropical eosinophilic asthma, 38
Forbes, G. B., and Strange, F. G., St. C. Tuberculous abscess following penicillin injection, 35
Forman, A. See Levine, E. R., *et al.*
Forney, J. E., and Raffel, S. Bacillary wax and delayed hypersensitivity, 29
Fouquet, M. J., Heimann, V., Meyer, M., and Hennequet. Streptomycin for tuberculous meningitis, 70
Fracture of rib. See Rib fracture.
Fréour, P. See Damade, P., *et al.*
Fridjohn, L., and Azzopardi, P. G. Spontaneous mediastinal emphysema, 69
Friedlander's pneumonia in infants, 52
Fundi during streptomycin therapy, 7
Fungous infection, Dual, 22
Furacin, Tuberculostatic effect of, 73
Furcolow, M., and Bunnell, I. Histoplasmosis 21
——, Engel, M., and Bunnell, I. Depression of tuberculin sensitivity, 33

Galdston, M., and Horwitz, S. A. Gas exchange in respiratory dead space, 77
Galland, M. Streptomycin for bone and joint tuberculosis, 71
Galy, P., Berard, M., and Dumarest, J. Tuberculoma of the lung, 34
Gangrene from grass, 57
Gardner, E., and Jacobs, J. Joint reflexes and respiration, 15
Garland, L. H. Interpretation of roentgenograms, 51
Gas exchange in respiratory dead space, 77
Gelenger, S. M., and Wiggers, R. F. Pleural fluid sugar, 28
Gelfand, M. L. Spontaneous rib fracture, 68
Gerard-Marchand, P. Streptomycin for bone and joint tuberculosis, 71
Gerber, I. E., and Potter, B. P. Interstitial fibrosis of lungs, 40
Gernez-Rieux, Ch., Breton, A., and Sevin, A. Bronchial washings, 5
Gilbert, J. G., Aronoff, J. S., and Rosen, D. M. Otolaryngological tuberculosis, 7
Gillard, M., and LeCocq, A. Loss of tuberculin sensitivity, 31
Ginés, A. R., Gould, E., and Talavera, C. R. Effect of amount of tuberculin, 31

Gobbel, W. G., Jr. Oil pneumonia, 62
Goodman, J., and Mann, Ch. Fluid shifts in pressure breathing, 76
Gould, E. See Ginés, A. R., *et al.*
Goyer, L. See Bernou, A., *et al.*
Gragsted, I. Avian tuberculosis, 65
Grant, A. R., House, R. K., and Crandell, W. B. Eosinophilic granuloma of rib, 37
Granuloma, eosinophilic, of rib, 37
Granulomatosis, lipoid, 54
Grekin, R. H., and Curtis, A. C. Sarcoidosis, 22
Grenville-Mathers, R. Rehabilitation of tuberculous patients, 80
Grinchar, I. N. Lupus and bone tuberculosis, 65
Grotts, B. F. Friedlander's pneumonia in infants, 52
Gugle, L. J. See Chapman, D. W., *et al.*
Gumpert, T. E. Appearance of lungs in mitral stenosis, 53

Haduroy, P., and Rosset, W. Rapid streptomycin sensitivity test, 30
Hales, M. R., See Liebow, A. A., *et al.*
Hall, J. H. See Rosemond, G. P., *et al.*
——, W. C. Hamartoma of lung, 57
Hamartoma of lung, 57
——E., and Crinker, C. K. Pulmonary edema due to ANTU, 75
Hardenbergh, Esther. See Sarnoff, S. J., *et al.*
Harrison, W. See Bloomer, W. E., *et al.*
Hasler, H. Follow-up of collapse therapy, 50
Haynes, Florence W. See Hellems, H. K., *et al.*
Heimann, V. See Fouquet, M. J., *et al.*
Helander, S., and Alin, K. Tissue distribution of PAS, 30
Hellems, H. K., Haynes, Florence W., Dexter, L., and Kinney, Th. D. Pulmonary capillary pressure, 14
Hemothorax after pneumonolysis, 2
Hennequet. See Fouquet, M. J., *et al.*
Heyman, A. See Sheldon, W. H., *et al.*
Hiatt, W. O. See Spicer, C. *et al.*
Hightower, J. A. See Woodward, T. E., *et al.*
Hill, W. T. Scoliosis and cardiac failure, 37
Hinkel, C. L. Unresolved pneumonia, 54
Hirschl, D., Levy, H., and Litvak, A. M. Streptomycin frugality, 27
Histopathology of bronchiectasis, 23
Histoplasmosis, 21
—— in California, 53
Hoar, C. S., and Terrell, C. O., Jr. Streptomycin for pneumonia, 28
Hodes, P. J., Johnson, J., and Atkins, J. P. Traumatic bronchial rupture, 58
Holbrook, W. A. See Woodward, T. E., *et al.*
Horacheck, J. Calciferol for skin tuberculosis, 66
Horwitz, S. A., and Galdston, M. Gas exchange in expiratory dead space, 77
House, R. K. See Grant, A. R., *et al.*
Huang, C., and Stone, M. Chest wall tuberculosis, 35
Hubert, P. See Serée, R., *et al.*
Huebner, R. See Beck, M., *et al.*
Hug, R., Moeschlin, S., and Tanner, E. PAS for bronchial and urinary tuberculosis, 60
Humidity and air-borne bacteria, 12
—— —— influenza virus, 13
Hurst, A., and Bobrowitz, I. D. Minimal tuberculosis, 50
Hutchison, J. N. Bronchi in primary childhood tuberculosis, 33
Hyde, B., and Hyde, L. Coccidioidomycosis and tuberculosis, 66
——, L., and Hyde, B. Coccidioidomycosis and tuberculosis, 66
Hypersenstivity, delayed, and bacillary wax, 29

Infants, Friedlander's pneumonia in, 52
Infarction, pulmonary, 76
Infection after pulmonary resection, 60
——, Bullous emphysema with, 23
——, fungus, dual, 22
——, tuberculous droplet, in rabbits, 11
Infections, respiratory, Streptomycin for, 73
Influenza virus and humidity, 13
Ingelrans, P., Vendeuvre, A., and Nigoul, J. Streptomycin for bone and joint tuberculosis, 71
Inhalation of penicillin dust, 8
Insulin tolerance in amyloidosis, 30
Intracellular bodies in sarcoidosis, 35
Intrapleural pneumonolysis. See Pneumonolysis, intrapleural
Irons, E. E. BCG for students, 63
Irritants, plastic, 30
Ivy, A. C. See Schwerma, H., *et al.*

Jackson, C. A. Toxic effects of pontocaine, 68
Jacobs, J., and Gardner, E. Joint reflexes and respiration, 15
Janauschek, K. Extrafascial tuberculosis, 1
——. Hemothorax after pneumonolysis, 2
Jellinek, K. Streptomycin for extrapulmonary tuberculosis, 43
Johnson, J. See Hodes, P. J., *et al.*

Joint reflexes and respiration, 15
Joules, E. A., and Nassau, E. Para-aminosalicylic acid for tuberculosis, 59
Jordan, J. W., and Spencer, H. Congenital tuberculosis, 65
Judge, D. J., Rice, E. C., and Davis, E. W. Gangrene from grass, 57

Kaiser, K. Endothelium of the pleura, 25
Kappert, A. Bronchial adenoma, 5
Karp, M. See Krasno, L., *et al.*,
Kavee, J., and Stivelman, B. P. Putrid lung abscess, 24
Kelso, J. W., and Russo, P. E. Dysgerminoma, 56
Kessel, J. F. See Spicer, C., *et al.*
Kinetics of benzoic acid oxidation, 61
Kinney, Th. D. See Hellems, H. K., *et al.*
Kirchheimer, W. F. Weiser, R. L., and Van Liew, R. Transfer of systemic tuberculin sensitivity, 75
Klein, W. S. See Levine, E. R., *et al.*
Krasno, L., Karp, M., and Rhoads, P. S. Penicillin dust inhalation, 8
Kridelbaugh, W. W. See Mason, E. F., *et al.*

Labhart, A., and Rechenberg, H. Endobronchial tuberculosis, 18
Labourt, F. E. See Battro, A., *et al.*
Landau, N. Tuberculous pleural effusion, 17
Lapi, A. See Metcoff, J., *et al.*
Lardanchet, J. Pneumothorax for minimal tuberculosis, 1
LeBrigand, H., and Sweet, R. H. Relative safety of upper lobe lobectomy, 4
LeCocq, A., and Gillard, M. Loss of tuberculin sensitivity, 31
Lees, D. H. See Paulley, J. W., *et al.*
——, H. D. Tuberculosis among students, 64
Le Foyer, Bertheau, Pervés, and Sabiani. Streptomycin with extrapleural pneumothorax, 71
Lemoine, J. M., and de Léobardy, J. Circumscribed bronchitis, 67
Lesions, lung, Aspiration biopsy of, 56
Lester, W., Jr., Humidity and influenza virus, 13
Leukocyte blockade of tuberculin cytolysis, 75
Levaditi, C. Thiosemicarbazone in experimental tuberculosis, 74
Levine, E. R., Klein, W. S., and Forman, A. Streptomycin for tuberculosis, 8
Levrat, M., and Despierres, G. Paradoxical mediastinal swing in pleurisy, 2
Levy, H. See Hirschl, D., *et al.*
Lewis, H. D., and Altschule, M. D. Carbonic anhydrase in blood, 78
Liebow, A. A. See Bloomer, W. E., *et al.*
——, Hales, M. R., and Lindskog, G. E. Bronchial arteries in bronchiectasis, 61
Ligation of pulmonary artery, Respiration after, 76
Lind, H. E. Fluorescent microscopy of tubercle bacilli, 62
Lindskog, G. E. See Bloomer, W. E., *et al.*
——. See Liebow, A. A., *et al.*
Lipoid granulomatosis, 54
—— pneumonia. See Pneumonia, lipoid
Lister, W. A. Chronic bronchitis, 38
Litvak, A. M. See Hirschl, D., *et al.*
Lobe, upper, Relative safety of lobectomy of, 4
——, ——, Technique of lobectomy of, 3
Lobectomy and decortication, 2
——, upper lobe, Relative safety of, 4
——, ——, Technique of, 3
Lobes, upper, Pedicles of, 3
London, S. Insulin tolerance in amyloidosis, 30
Lotte, A. See Bérnard, E., *et al.*
Lung abscess, acute, 24
—— ——, putrid, 24
—— cancer, Cytologic diagnosis of, 55
——, Carcinoma of, 55
——, Hamartoma of, 57
—— lesions, Aspiration biopsy of, 56
—— resection for tuberculosis, 34
—— Tuberculoma of, 34
Lungs, appearance of, in mitral stenosis, 53
——, honeycomb, 21
——, interstitial fibrosis of, 40
Lupus and bone tuberculosis, 65
—— vulgaris, 26
Lymphogranuloma venereum, 37

MacRae, D. J. Spontaneous mediastinal emphysema, 69
Mann, Ch., and Goodman, J. Fluid shifts in pressure breathing, 76
Marceaux. See Bernou, A., *et al.*
Marks, J. L., and Nathan, A. Linear atelectasis, 53
Mason, E. F., Kridelbaugh, W. W., Crouch, W. H., and Ward, M. Streptomycin and tuberculous enteritis, 59
Mathey, J., and Maurer, A. Technique of upper lobe lobectomy, 3
—— and Monod. See Bérnard, E., *et al.*
Maurer, A., and Mathey, J. Technique of upper lobe lobectomy, 3
——, and Tobé, F. Pedicles of upper lobes, 3

McCable, A. M., and Cuttino, J. T. Granulomatous nocardiosis, 41
McCarter, J. R., and Bevilacqua, E. B. Tuberculoproteins, 11
McDonald, J. R., and Woolner, L. B. Sputum smears for carcinoma, 36
——, ——, Cytological examination of sputum, 25
McGrath, A. K. See Farber, S. M., *et al.*
McIntire, F. T., and Sykes, E. M. Obstruction of superior vena cava, 57
McMurray, B. Tuberculosis of greater trochanter, 18
Mediastinal swing. See Swing, mediastinal, 2
Medium, Dubos, for streptomycin sensitivity tests, 61
Meiklejohn, G., and Shragg, R. I. Aureomycin for primary atypical pneumonia, 73
Meningitis, Changes in, after streptomycin, 6
—— in children, therapy of, 7
——, tuberculous, Streptomycin for, 70
——, ——, streptomycin and streptokinase for, 42
Mental hospitals, Tuberculosis in, 79
Meredith, H. C., Jr. Streptomycin for tuberculous pericarditis, 7
Metcoff, J., Darling, D., Wilson, D., Lapi, A., and Stare, F. J. Nutrition and response to tuberculosis, 74
Methods, fluorescent, for smears, 9
Meyer, F. Fundi during streptomycin therapy, 7
——, M. See Fouquet, M. J., *et al.*
Michael, M. See Spendlove, G., *et al.*
Microscopy, fluorescent, of tubercle bacilli, 62
Middlebrook, G., and Dubos, R. J. Wetting agents and growth of tubercle bacilli, 10
Miescher, G. Erythema nodosum, 53
Miliary tuberculosis. See Tuberculosis, miliary
Miller, C. C., and Sweet, R. H. Infection after pulmonary resection, 60
Minimal tuberculosis. See tuberculosis, minimal
Mitchison, D. A., and Crofton, J. Streptomycin resistance, 6
Moeschlin, S. See Hug, R., *et al.*
Mohun, A. F., and Rubie, J. Streptomycin for tuberculous meningitis, 70
Mollov, M., and Oshinsky, A. Dubos medium for streptomycin sensitivity tests, 61
Monfajon, Ch. Alberet. See Bastide, J. *et al.*
Monod, O. Lung resection for tuberculosis, 34
——, R. See Bérnard, E., *et al.*
Morgan, H. E. See Finn, J. F., Jr., *et al.*
Mortality, tuberculous, and overcrowding, 62
Mounier-Kuhn, P., and Dufourt, A. Primary complex and bronchoscopy, 17
Mouse, white, in tuberculosis, 29
Mousel, L. H. Surgical treatment of bronchiectasis, 69
Müller, Jenny, and Pedrazzini, A. Sarcoidosis, 5
Muriel, A. Gomez. Fluorescent method for smears, 9
M. Ranae, Streptomycin-dependent, 74
M. tuberculosis, Streptomycin-enhanced, 44
Myers, J. A. Eradication of tuberculosis, 80

Nassau, E., and Joules, E. A. Para-aminosalicylic acid for tuberculosis, 59
Nathan, A., and Marks, J. L. Linear atelectasis, 53
Nigoul, J. See Ingelrans, P., *et al.*
Nocardiosis, granulomatous, 41

Obstruction of superior vena cava, 57
Oil pneumonia, 62
O'Keefe, J. J. Bronchogenic carcinoma, 36
Oosthuizen, S. F., and Fainsinger, N. H. Pulmonary actinomycosis, 41
Ornstein, G. G. Pulmonary emphysema, 23
Osborne, R. R. See Youmans, G. P., *et al.*
Oshinsky, A., and Mollov, M. Dubos medium for streptomycin sensitivity tests, 61
Oswald, N., and Parkinson, T. Honeycomb lungs, 22
Otolaryngological tuberculosis. See Tuberculosis, otolaryngological,
Overcrowding and tuberculous mortality, 62
Overholt, R. H., and Schmidt, I. C. Carcinoma of lung, 55
Oxidation of benzoic acid, Kinetics of, 61

Padavani, P. See Bérnard, E., *et al.*
Painter, S. L. Tuberculosis in children, 49
Pan, S. C., Chih, C. S., and Chien, Y. P. Thymoma, 37
Para-aminosalicylic acid for tuberculosis, 26, 59
PAS for bronchial and urinary tuberculosis, 60
——, Tissue distribition of, 30
Parkinson, T., and Oswald, N. Honeycomb lungs, 22
Paulley, J. W., Lees, D. H., and Pearson, A. C. Rib fracture from coughing during pregnancy, 68
Pearson, A. C. See Paulley, J. W., *et al.*
Pedicles of upper lobes, 3
Pedrazzini, A., and Müller, Jenny. Sarcoidosis, 5

Penicillin dust inhalation, 8
—— injection followed by tuberculous abscess, 35
Pericarditis, constrictive, 19
——, tuberculous , Streptomycin for, 7
Perr, H., and Beham, H. Streptomycin stomatitis, 8
Pertussis, Streptomycin for, 27
Pervés. See LeFoyer, *et al.*
Pfister, H. O., and Schwarz, W. Photofluorography, 16
Photofluorography, 16
Pickering, G. W. See Andrews, G. W. S., *et al.*
Piéchaud, F. See Damade, P., *et al.*
Pietrafesa, E. See Battro, A., *et al.*
Pirani, C. L., Ewart, F. E., Jr., and Wilson, A. L. Mycolic pulmonary arterial aneurysms, 54
Plastic irritants, 30
Pleura, Endothelium of, 25
——, Role of, in pneumonectomy, 19
Pleural fluid sugar, 28
Pleurisy, paradoxical mediastinal swing in, 2
Pleurodynia, epidemic, 38
Pneumoconiosis, bauxite-fume, 67
Pneumonectomy, Role of pleura in, 19
Pneumonia, atypical, Aureomycin for, 28
——, Friedlander's, in infants, 52
—— in hemolytic anemia, 37
——, interstitial, in dogs, 42
——, lipoid, 39
——, oil, 62
——, primary atypical, Aureomycin for, 73
——, Streptomycin for, 28
——, unresolved, 54
Pneumonitis, beryllium, 51
—— following bronchography, 40
——, primary, 22
Pneumonolysis, early intrapleural, 19
——, Hemothorax after, 2
Pneumothorax, extrafascial, 1
——, extrapleural, Streptomycin with, 71
—— for minimal tuberculosis, 1
——, initial, 49
Pollution, industrial, atmosphric, 32
Pontocaine, Toxic effects of, 68
Potter, B. P., and Gerber, I. E. Interstitial fibrosis of lungs, 40
Prchal, C. J. Coccidioidomycosis of cattle, 42
Pregnancy, rib fracture during, 68
Pressure breathing, Fluid shifts in, 76
——, intercranial, and pulmonary edema, 76
Prevention of tuberculosis, 15
Pryor, Helen B. Histoplasmosis in California, 53
Psittacosis, Complement fixation in, 12
Puck, T. T., and Dunklin, E. W. Humidity and air-borne bacteria, 12
Pulaski, E. J., and White, Th. T. Streptomycin for respiratory infections, 73
Pulmonary adenomatosis. See Adenomatosis, pulmonary
—— edema. See Edema, pulmonary.
—— embolism. See Embolism, pulmonary
—— emphysema. See Emphysema, pulmonary.
—— eosinophilosis. See Eosinophilosis, pulmonary

Q Fever, 32

Rabbits, Tuberculous droplet infection in, 11
Raby, W. T. See Woodward, T. E., *et al.*
Raffel, S., and Forney, J. E. Bacillary wax and delayed hypersensitivity, 29
Ragaz, L. Para-aminosalicylic acid, 26
Ratcliffe, H. L., and Wells, W. F. Tuberculous droplet infection in rabbits, 11
Rather, L. J. Pneumonia in hemolytic anemia, 37
Rechenberg, H., and Labhart, A. Endobronchial tuberculosis, 18
Reflexes, joint, and respiration, 15
Rehabilitation of tuberculous patients, 80
Resection of lung for tuberculosis, 34
——, pulmonary, Infection after, 60
Resistance, streptomycin, 6
Respiration and blood pressure, 14
—— after pulmonary artery ligation, 76
—— and joint reflexes, 15
——, artificial, 14
Respiratory dead space, Gas exchange in, 77
Rhoads, P. S. See Krasno, L., *et al.*
Rib, Eosinophilic granuloma of, 37
—— fracture from coughing, 66
—— —— from coughing during pregnancy, 68
—— ——, spontaneous, 68
Rice, E. C. See Judge, D. J., *et al.*
Riddell, A. C. R., and Wyatt, J. P. Bauxite-fume pneumoconiosis, 67
Rigler, L., and Shapiro, R. Pulmonary embolism, 54
Robbins, L. L. Idiopathic pulmonary fibrosis, 40
Robitzek, E. H. See Selikoff, I. J., *et al.*
Roentgenograms, Interpretation of, 51
Rosemond, G. P., Burnett, W. E., and Hall, J. H. Aspiration biopsy of lung lesions, 56
Rosen, D. M. See Gilbert, J. G.

Rosenthal, J., and Feigin, I. Boeck's sarcoid, 2
Rosset, W., and Haduroy, P. Rapid streptomycin sensitivity test, 30
Roussel, P. See Bastide, J., *et al.*
Roux, M. See Damade, P., *et al.*
Rubie, J., and Mohun, A. F. Streptomycin for tuberculous meningitis, 70
Rupture, traumatic bronchial, 58
Russo, P. E., and Kelso, J. W. Dysgerminoma, 56
Ruzicka, O. Streptomycin for miliary tuberculosis, 7

Sabiani. See Le Foyer, *et al.*
Sarcoid, Boeck's, 2
Sarcoidosis, 5, 22
—— and tuberculosis, 20
——, Intracellular bodies in, 35
——, Serology of, 36
Sarnoff, S. J., Hardenbergh, Esther, and Whittenberger, J. L. Artificial respiration, 14
Sarot, I. A. Decortication and lobectomy, 2
——. Massive pleural tumor, 57
Scheiner, Z., and Cara, M. Experimental pulmonary atelectasis, 77
Schmidt, I. C., and Overholt, R. H. Carcinoma of lung, 55
Schneider, L. Lipoid pneumonia, 39
——, M. See Schwartzman, J., *et al.*
Schneierson, S. J., and Schneider, L. Lipoid granulomatosis, 54
Schoenbach, E. B., and Bryer, M. S. Aureomycin for atypical pneumonia, 28
Schomer, A. See Bass, H. E., *et al.*
Schwabacher, H., Wilinson, R. H., Karran, C. W. C. Streptomycin for pertussis, 27
Schwartzman, J., Schneider, M., and Crusius, M. E. Tuberculin sensitization, 19
Schwarz, W., and Pfister, H. O. Photofluorography, 16
Schwerma, H., Ivy, A. C., Burkhardt, W. L., and Thometz, A. F. Resuscitation from obstructive asphyxia, 76
Scoliosis and cardiac failure, 37
Scremini, A. Pérez. See Blanch, H. Cantonnet, *et al.*, 20
Secrétan, M. Dangers of vitamin D_2 therapy, 1
Seiler, M. Para-aminosalicylic acid for tuberculosis, 26
Selikoff, I. A., and Tchertkoff, I. G. Role of pleura in pneumonectomy, 19
——, Tchertkoff, I. G., and Robitzek, E. H. Initial pneumothorax, 49
Sellors, T. H. See Andrews, G. W. S., *et al.*
Sensitivity, tuberculin, Depression of, 33
——, ——, Loss of, 31
Sensitization, Tuberculin, 19
Serée, R., Dettloff, H., Hubert, P., and Verney, H. Streptomycin for bone and joint tuberculosis, 71
Serology of sarcoidosis, 36
Sevin, A. See Gernez-Rieux, Ch., *et al.*
Shapiro, R., and Rigler, L. Pulmonary embolism, 54
Shatz, B. A. See Bergman, M., *et al.*
Shaw, E. See Beck, M., *et al.*
——, R. R. Thoracic complications of amebiasis, 52
Sheldon, J. M. Fluids for bronchial asthma, 38
——, W. H., Wall, M. J., Slade, J. deR., and Heyman, A. Lymphogranuloma venereum, 37
Shillen, J. Industrial atmospheric pollution, 32
Shragg, R. I., and Meiklejohn, G. Aureomycin for primary atypical pneumonia, 73
Slade, J. DeR. See Sheldon, W. H., *et al.*
Smears, Fluorescent, method for, 9
——, sputum, for carcinoma, 36
Solomidès, J. Culture of tubercle bacilli, 75
——. See Valtis, J., *et al.*
Sorrel-Dejerine, and Sorrel, M. E. Streptomycin for bone and joint tuberculosis, 71
Sorrel, M. E., and Sorrel-Dejerine. Streptomycin for bone and joint tuberculosis, 71
Southworth, J. L. Plastic irritants, 30
Spencer, H., and Jordan, J. W. Congenital tuberculosis, 65
Spendlove, G., Cummings, M., Fackler, W., and Michael, M. Streptomycin-enhanced *M. tuberculosis*, 44
Sphingomyelin and growth of tubercle bacilli, 10
Spicer, C., Hiatt, W. O. and Kessel, J. F. Dual fungous infection, 22
Sputum concentration, 8
——, Cytological examination of, 25
—— smears. See Smears, sputum
——, Tumor cells in, 5
Stare, F. J. See Metcoff, J., *et al.*
Steenken, W., Jr. See Wolinsky, E., *et al.*
Stein, S. C. See Cochrane, A. L., *et al*,
Steinberg, I., and Dotter, C. T. Angiocardiography of great vessels, 58
Steinlin, H. PAS for tuberculosis, 26
Stenosis, mitral, Appearance of lungs in, 53
Stevenson, G. F., and Stevenson, F. L. Pulmonary embolism, 22

Stevenson, F. L., and Stevenson, G. F. Pulmonary embolism, 22
Stivelman, B. P., and Kavee, J. Putrid lung abscess, 24
Stomatitis, streptomycin, 8
Stone, M., and Huang, C. Chest wall tuberculosis, 35
Strange, F. G. St. C., and Forbes, G. B. Tuberculous abscess following penicillin injection, 35
Streptokinase and streptomycin for tuberculous meningitis, 42
Streptomycin and clotting time, 59
—— —— streptokinase for tuberculous meningitis, 42
—— —— surgery, 72
——, Changes in meningitis after, 6
——dependent *M. Ranae*, 74
——enhanced *M. tuberculosis*, 44
—— for bone and joint tuberculosis, 71
—— —— enteric tuberculosis, 71
—— —— extrapulmonary tuberculosis, 43
—— —— miliary tuberculosis, 7
—— —— pertussis, 27
—— —— pneumonia, 28
—— —— respiratory infections, 73
—— —— tuberculous endometritis, 43
—— —— —— enteritis, 43, 59
—— —— —— meningitis, 70
—— —— —— pericarditis, 7
—— —— tuberculosis, 8
—— frugality, 27
—— resistance, 6
—— —— of tubercle bacilli, 72
——-resistant tubercle bacilli, 44
—— sensitivity, Test of, 74
—— —— —— rapid, 30
—— —— tests, Dubos medium for, 61
—— stomatitis, 8
—— therapy, Fundi during, 7
—— with antihistaminic drugs, 27
—— —— extrapleural pneumothroax, 71
—— —— Vitamin B deficiency, 27
Students, BCG for, 63
——, Tuberculosis among, 64
Sugar, pleural fluid, 28
Sumner, J. Vitamin B deficiency with streptomycin, 27
Surgery and streptomycin, 72
Survey, mass, 63
Sweany, H. C. See Drymalski, G. W., *et al.*
Swedberg, B. White mouse in tuberculosis, 29
Sweet, R. H., and LeBrigand, H. Relative safety of upper lobe lobectomy, 4
Sweet, and Miller, C. C. Infection after pulmonary resection, 60
Swing, mediastinal, in pleurisy, 2
Sykes, E. M., and McIntire, F. T. Obstruction of superior vena cava, 57

Talavera, C. R. See Ginés, A. R., *et al.*
T'ang, B. H. Y. Tuberculous empyema, 35
Tanner, E. See Hug, R., *et al.*
Tattersall, W. Relapse in pulmonary tuberculosis, 80
Tchertkoff, I. G., and Selikoff, I. A. Role of pleura in pneumonectomy, 19
——. See Selikoff, I. J., *et al.*
Teilum, G. Intracellular bodies in sarcoidosis, 35
Terrell, C. O., Jr., and Hoar, C. S. Streptomycin for pneumonia, 28
Test, rapid, of streptomycin sensitivity, 30
Tests for streptomycin sensitivity, Dubos medium for, 61
Therapy, collapse, Follow-up of, 50
—— of meningitis in children, 7
——, streptomycin, Fundi during, 7
——, Vitamin D_2, Dangers of, 1
Thiosemicarbazone in experimental tuberculosis, 74
Thometz, A. F. See Schwerma, H., *et al.*
Thompson, J. R. See Drymalski, G. W., *et al.*
Thoracic complications of amebiasis, 52
Thymoma, 37
Tison, F. Sputum concentration, 8
Tissue distribution of PAS, 30
Tobé, F., and Maurer, A. Pedicles of upper lobes, 3
Tolerance of insulin in amyloidosis, 30
Traissac, F. J. See Damade, P., *et al.*
Tricoire, J. See Bernou, A., *et al.*
Trocanter, greater, Tuberculosis of, 18
Tubercle bacilli. See Bacilli, tubercle
Tuberculin, Effect of amount of, 31
—— sensitivity, Depression of, 33
—— —— Loss of, 31
—— ——, systemic, Transfer of, 75
—— sensitization, 19
Tuberculoma of the lung, 34
Tuberculoproteins, 11
Tuberculosis among students, 64
—— and coccidioidomycosis, 66
—— —— sarcoidosis, 20
——, avian, 65
——, basal, 50
——, bone, and lupus, 65
——, bronchial, PAS for, 60
——, congenital, 65

Tuberculosis control, 79
——, endobronchial, 18
——, Eradication of, 80
——, enteric, Streptomycin for, 71
——, experimental, Thiosemicarbazone in, 74
——, extrapulmonary, Streptomycin for, 43
—— in Belgian Congo, 78
—— —— childhood, Bronchi in, 33
—— —— children, 49
—— —— mental hospitals, 79
——, Laboratory diagnosis of, 9
——, Lung resection for, 34
——, miliary, Streptomycin for, 7
——, minimal, Pneumothorax for, 1
——, ——, Prognosis of, 50
——, nutrition and response to, 74
—— of bone and joint, Streptomycin for, 71
—— —— chest wall, 35
—— —— greater trochanter, 18
—— —— the skin, Calciferol for, 66
——, Otolaryngological, 7
——, Para-aminosalicylic acid for, 26, 59
——, Prevention of, 15
——, pulmonary, Relapse in, 79
——, Streptomycin for, 8
——, urinary, PAS for, 60
——, white mouse in, 29
—— with Addison's disease, 44
Tuberculous abscess. See Abscess, tuberculous
—— droplet. See Droplet, tuberculous
—— empyema. See Empyema, tuberculous
Tularemia, Aureomycin for, 73
Tumor cells in sputum, 5
——, massive pleural, 57

Vaccination, BCG, Complications of, 20
——, Contact control during, 32
—— with vole bacillus, 78
Valtis, J., van Deinse, F., and Solomides, J. Cultures in Dubos medium, 8
van Deinse, F. See Valtis, J., *et al.*
Vanderlinde, R. J., and Yegian, D. Streptomycin-dependent *M. Ranae*, 74
Van Liew, R. See Kirchheimer, W. F., *et al.*
Variations in virulence of BCG, 29
Vena cava, superior, Obstruction of, 57
Vendeuvre, A. See Inglerans, P., *et al.*
Verney, H. See Serée, R., *et al.*
Virulence variations of BCG, 29
Visscher, M. B., and Campbell, G. S. Pulmonary edema and intracranial pressure, 76
Vitamin B deficiency with streptomycin, 27
Vitamin D_2 Therapy, Dangers of, 1
Vole bacillus. See Bacillus vole
—— tubercle bacilli, See Bacilli, vole tubercle.

Wall, M. J. See Sheldon, W. H., *et al.*
Wallgren, A. Contact control during vaccination, 32
Ward, M. See Mason, E. F., *et al.*
Washings, Bronchial, 5
Wax, bacillary, and delayed hypersensitivity, 29
Weber, F. J., and Anderson, F. J. Tuberculosis control, 79
Weill, J. See Bérnard, E., *et al.*
Weiser, R. L. See Kirchheimer, W. F., *et al.*
Weller, Th. See Finn, J. F., Jr., *et al.*
Wells, A. G. Vaccination with vole bacillus, 78
——, A. Q., and Wylie, J. A. H. Serology of sarcoidosis, 36
——, W. F., and Ratcliffe, H. L. Tuberculous droplet infection in rabbits, 11
Wetting agents and growth of tubercle acilli, 10
Wetzel, V. See Wolinsky, E., *et al.*
Wheeler, P. W. See Chapman, D. W., *et al.*
White, Th. T., and Pulaski, E. J. Streptomycin for respiratory infections, 73
Whittenberger, J. L. See Sarnoff, S. J., *et al.*
Wiggers, R. F., and Gelenger, S. M. Pleural fluid sugar, 28
Willcox, A., and Colson, G. M., Bronchogenic carcinoma, 69
Williston, E. H. See Youmans, G. P., *et al.*
Wilson, A. L. See Pirani, C. L., *et al.*
——, D. See Metcoff, J., *et al.*
Wiswanathan, V. Pulmonary eosinophilosis, 20
Wolinsky, E., Wetzel, V., and Steenken, W., Jr. Tuberculostatic effect of Furacin, 73
Woodward, T. E., Raby, W. T., Eppes, W., Holbrook, W. A., and Hightower, J. A. Aureomycin for tularemia, 73
Woolner, L. B., and McDonald, J. R. Cytological examination of sputum, 25
—— —— ——. Sputum smears for carcinoma, 36
Wyatt, J. P., and Riddell, A. C. R. Bauxite-fume pneumoconiosis, 67
Wylie, J. A. H., and Wells, A. Q. Serology of sarcoidosis, 36

Yegian, D., and Vanderlinde, R. J. Streptomycin-dependent *M. Ranae*, 74
Youmans, G. P., Williston, E. H., and Osborne, R. R. Streptomycin-resistant tubercle bacilli, 44

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF THE AMERICAN TRUDEAU SOCIETY
Medical Section of National Tuberculosis Association

ABSTRACTS

EDITOR-IN-CHIEF
ESMOND R. LONG
Philadelphia, Pa.

MANAGING EDITOR
WALSH MCDERMOTT
New York, N. Y.

EDITORIAL BOARD

W. EDWARD CHAMBERLAIN, Philadelphia, Pa.
HALBERT L. DUNN, Washington, D. C.
H. CORWIN HINSHAW, San Francisco, Calif.
KIRBY S. HOWLETT, JR., Shelton, Conn.
JOHN C. JONES, Los Angeles, Calif.
ALEXANDER D. LANGMUIR, Baltimore, Md.
HERBERT C. MAIER, New York, N. Y.
WILLIAM P. SHEPARD, San Francisco, Calif.
C. EUGENE WOODRUFF, Northville, Mich.

VOLUME 60

JULY-DECEMBER, 1949

PUBLISHED MONTHLY

AT MOUNT ROYAL AND GUILFORD AVENUES, BALTIMORE 2, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS: ORIGINAL ARTICLES

NUMBER 1, JULY, 1949

Late Nontuberculous Complications of Calcified Hilus Lymph Nodes. JEROME R. HEAD AND CHESTER W. MOEN 1

Observations on Lower Lobe Disease in Pulmonary Tuberculosis. J. R. VIVAS AND C. A. LAUBACH, JR. 15

Insulin in the Treatment of Tuberculous Patients with Anorexia—A Modified Technique. PHILIP MORGENSTERN AND STEPHEN B. DEWING 25

Tuberculosis of the Trachea and Major Bronchi. Results of Treatment with Streptomycin. ARTHUR M. OLSEN AND H. CORWIN HINSHAW 32

Toxicity of Streptomycin for the Auditory and Vestibular Mechanisms. EDMUND P. FOWLER, JR. AND CARL R. FEIND 39

Repeated Transcutaneous Autolytic Tuberculin Tests in Children. WM. WILEY JONES, CLARENCE NELSON, AND RALPH E. DWORK 45

A Slide Culture Method for the Early Detection and Observation of Growth of the Tubercle Bacillus. A Preliminary Report. J. W. BERRY AND HOPE LOWRY 51

The Pharmacologic and Chemotherapeutic Action of Some New Sulfones and Streptomycin in Experimental Tuberculosis. M. I. SMITH, E. L. JACKSON, J. M. JUNGE, AND B. K. BHATTACHARYA 62

Neomycin Activity upon *Mycobacterium Tuberculosis* and Other Mycobacteria. SELMAN A. WAKSMAN, DORRIS HUTCHISON, AND EDWARD KATZ 78

The Use of the Mouse in a Standardized Test for Antituberculous Activity of Compounds of Natural or Synthetic Origin. I. Choice and Standardization of Culture. CLARA M. MCKEE, GEOFFREY RAKE, RICHARD DONOVICK, AND WILLIAM P. JAMBOR 90

The Use of the Mouse in a Standardized Test for Antituberculous Activity of Compounds of Natural or Synthetic Origin. II. Choice of Mouse Strain. RICHARD DONOVICK, CLARA M. MCKEE, WILLIAM P. JAMBOR, AND GEOFFREY RAKE 109

The Use of the Mouse in a Standardized Test for Antituberculous Activity of Compounds of Natural or Synthetic Origin. III. The Standardized Test. GEOFFREY RAKE, WILLIAM P. JAMBOR, CLARA M. MCKEE, FELIX PANSY, FREDERICK Y. WISELOGLE, AND RICHARD DONOVICK 121

The Use of Biometric Methods in Comparison of Acid-fast Allergens. F. M. WADLEY 131

Editorial: Tuberculosis in Medical Teaching. CARL MUSCHENHEIM 140

Letters to the Editors: Tuberculostatic Activity of Aureomycin *in vitro* and *in vivo*. GEOFFREY RAKE AND RICHARD DONOVICK 143

Books 144

Abstracts 1

NUMBER 2, AUGUST, 1949

Simple Tests of Ventilatory Function for Use in the Sanatorium or Clinic. FREDERICK C. WARRING, JR. 149
Phrenic Nerve Interruption in the Treatment of Pulmonary Tuberculosis. II. Complications and Sequelae of Phreniclasis. ROGER S. MITCHELL 168
Phrenic Nerve Interruption in the Treatment of Pulmonary Tuberculosis. III. The Effect of a Paralyzed Hemidiaphragm on the Results of Homolateral Thoracoplasty. ROGER S. MITCHELL 183
Physical Therapy in Postthoracoplasty. One Year's Notes and Observations. JACOB GOLDBERG, RALPH FRIEDLANDER, HARRY B. DOPPELT, AND DOROTHY E. MILLER 189
Concerning the Location of Pulmonary Infarction. EUGENE I. ZINS 206

Factors Affecting the *in vitro* Cytolysis of White Blood Cells by Tuberculin. CUTTING B. FAVOUR, PAUL FREMONT-SMITH, AND JOSEPH M. MILLER 212
A Simplified Guinea Pig Test for Tuberculostatic Agents. F. I. DESSAU, R. L. YEAGER, AND M. KULISH 223
An Evaluation of a Method of Obtaining Gastric Washings. JAMES B. HOLLOWAY, JR. AND MARTIN CUMMINGS 228
Case Reports:
Pathological and Experimental Studies of Boeck's Sarcoid. 1. Report of a Case with Panarteritis, Periarteritis, Terminal-hypertension and Uremia, and the Reproduction of a Sarcoid-like Lesion in Guinea Pigs. SOL ROY ROSENTHAL 236
Erythema Induratum Bazin. Report of a Proved Case Associated with Tuberculous Lymphadenitis, Completely Relieved by Tuberculin Desensitization. THEODORE T. FOX, HENRY L. JAFFE, AND LOUIS LICHTENSTEIN 249
Pulmonary Adenomatosis. Report of a Case. BENJAMIN FREEDMAN 258
Editorial: Integration of Streptomycin with other Forms of Therapy for Pulmonary Tuberculosis. JOHN O'CONNOR 264
Letters to the Editors: A Pyridine Derivative and Experimental Tuberculosis. H. J. CORPER, MAURICE L. COHN, AND WM. H. FREY 269
Abstracts 17

NUMBER 3, SEPTEMBER 1949

Influence of Type of Disease on the Results of Thoracoplasty in Pulmonary Tuberculosis. MORRIS RUBIN AND ROBERT KLOPSTOCK 273
Pleural Decortication in Pulmonary Tuberculosis. JOSEPH WEINBERG AND J. DWIGHT DAVIS 288
Tuberculosis in Nurses: Clinical Observations on its Pathogenesis as Seen in a Fifteen-Year Follow-up of 745 Nurses. THEODORE L. BADGER AND L. FRED AYVAZIAN 305
The Problem of Tuberculosis Control among American Negroes. HOWARD M. PAYNE 332

Streptomycin Therapy of Tuberculous Pneumonia in Negro Adults. WILLIAM M. M. KIRBY, ROBERT M. SIMPSON, AND WILLIAM P. CREGER 343
The Effect of Antihistamine Medication on the Tuberculin Reaction in Children. ELI FRIEDMAN AND IRVING SILVERMAN 354
Chemotherapy of Murine Leprosy. CHARLES M. CARPENTER, HERBERT E. STOKINGER, LEIF G. SUHRLAND, AND HELEN ACKERMAN 359
The Evaluation of Antituberculous Agents with Avian Tuberculosis in Chicks: A Comparison of Dihydrostreptomycin and Streptomycin. MORRIS SOLOTOROVSKY, HENRY SIEGEL, ELIZABETH J. BUGIE, AND FRANCIS J. GREGORY 366
Routine Chest Photo-roentgenography in Baroness Erlanger Hospital, Chattanooga, Tennessee. PAUL M. GOLLEY 377
Editorial: The Necessity for Accurate Evaluation of the Results of Thoracoplasty. JOHN D. STEELE 383
Letters to the Editors:
The Effect of Ammonium Ions and Aliphatic Amines on the Ability of Virulent Mycobacteria to Bind Neutral Red. RENÉ J. DUBOS AND EMMANUEL SUTER 384
Toxic Effects of DL Serine on Virulent Human Tubercle Bacilli. RENÉ J. DUBOS 385
Intravenous Administration of P-aminosalicylic Acid. WILLIAM R. BARCLAY 385
Obituaries:
STRACHIMER A. PETROFF, 1883–1948 387
GEORGE CHAMBERS ANGLIN, 1890–1948 388
Books 389
Abstracts 33

NUMBER 4, OCTOBER, 1949

The Cost of Research on Tuberculosis in the United States. Analysis of Allocations in 1947–1948. VIRGINIA CAMERON 393
The Resected Postthoracoplasty Lung. A Clinico-pathologic Correlation. W. A. MEISSNER, R. H. OVERHOLT, N. J. WILSON, AND J. H. WALKER .. 406
Tumors of the Mediastinum. A Discussion of Diagnostic Procedure and Surgical Treatment Based on Experience with Forty-four Operated Cases. LYMAN A. BREWER, III, AND FRANK S. DOLLEY 419
The Urinary Excretion of Amino Acids: I. By Normal Male Subjects on Controlled Low- and High-protein Diets. M. S. DUNN, M. N. CAMIEN, S. AKAWIE, R. B. MALIN, S. EIDUSON, H. R. GETZ, AND K. R. DUNN ... 439
The Urinary Excretion of Amino Acids: II. By Tuberculous Male Subjects on Controlled Low- and High-protein Diets, K. R. DUNN, H. R. GETZ, M. S. DUNN, M. N. CAMIEN, S. AKAWIE, R. B. MALIN AND S. EIDUSON . 448
Studies of Food Intake and Requirements of Women with Active and Arrested Tuberculosis. W. D. BREWER, D. C. CEDERQUIST, C. J. STRINGER, AND M. A. OHLSON 455

An Appraisal of the Contribution of Mass Radiography in the Discovery of Pulmonary Tuberculosis. CHARLOTTE SILVERMAN 466
The Suitable Dose of Tuberculin for Single Test Tuberculin Testing. KUANG-YUAN LIU, HSIEN-CHIH KU, AND PHILIP T. Y. CH'IU 483
Disposition and Follow-up of Pulmonary Tuberculosis. A Study Based on the Character and Extent of the Lesion Seen on the Initial Roentgenogram. HAYNES HAROLD FELLOWS, JOHN A. EVANS, AND MARGARET G. STEPHENS 487
Miniature Chest Roentgenograms in Schools and Industries in San Antonio, Texas. P. A. PAMPLONA AND W. F. HAMILTON 501
Case Reports:
Miliary Tuberculosis Caused by Intravenous Self-injection of Tubercle Bacilli, Treated Successfully with Streptomycin Therapy. OSWALD R. JONES, WARREN D. PLATT, AND LUIS A. AMILL 514
Abdominal Pneumocele following Artificial Pneumoperitoneum. H. C. WORTMAN AND H. E. BASS 520
Pneumoperitoneum Complicated by Inguinal Hernia. Report of a Case. WILLIAM J. MCAULIFFE AND RICHMOND DOUGLASS 524
Editorial: The Cost of Tuberculosis Research. ESMOND R. LONG 527
Letters to the Editors:
What's Wrong with "Mass X-ray Surveys?" F. KENNETH ALBRECHT .. 532
Roentgenograms of Diffuse Pulmonary Lesions. DONALD S. KING 536
On the Action of Thiosemicarbazones in Experimental Tuberculosis in the Mouse. R. DONOVICK AND J. BERNSTEIN 539
Abstracts 49

NUMBER 5, NOVEMBER, 1949

Variation in the Duration of Tuberculin Skin Sensitivity Produced by Two Strains of BCG. RALPH F. JACOX AND GORDON M. MEADE 541
Correlation of Numbers of Cutaneous BCG Vaccination Papules and Subsequent Tuberculin Allergy and Tuberculosis Resistance in Guinea Pigs. KONRAD BIRKHAUG 547
Lung Trauma at Pneumothorax Induction. ALFRED S. DOONEIEF AND RUTH W. PICCAGLI 557
A Clinical Study of the Toxic Effects of Dihydrostreptomycin and Streptomycin. CHARLES M. DOMON, PHILLIP C. KILBOURNE, AND ERNEST Q. KING 564
Streptomycin Treatment of Tuberculous Enterocolitis. HENRY C. SWEANY, M. R. LICHTENSTEIN, GEORGE C. TURNER, AND LEROY BERARD 576
Rasmussen's Aneurysms and Fatal Hemorrhage in Pulmonary Tuberculosis. VIRGIL A. PLESSINGER AND PAUL N. JOLLY 589
Tuberculosis of the Trachea and Major Bronchi. OSCAR AUERBACH 604
Preservation of Mycobacteria by Desiccation *in vacuo*. M. FROBISHER, JR., G. C. KLEIN, AND M. M. CUMMINGS 621

Toxicity of Sputum Digestants to Tubercle Bacilli in Water and Sputum. GEORGE A. SPENDLOVE, MARTIN M. CUMMINGS, AND ROBERT A. PATNODE 628

The Combined Use of Tracheal Lavage and Culture as a Diagnostic Procedure in Pulmonary Tuberculosis. BUFORD H. WARDRIP, C. GERALD SCARBOROUGH, AND E. GWYN ROBERTS 634

Auscultation: A New Conception of the Respiratory Murmur and its Place in Diagnosis. F. M. POTTENGER 639

Case Reports:

Treatment of Acute Obstructive Tuberculous Enterocolitis by "Nonsurgical Ileostomy" and Streptomycin. JOHN W. WOODBURY AND SAMUEL PHILLIPS 648

A Case of Massive Hemothorax Complicating Therapeutic Pneumothorax. H. M. HOLDEN 654

Polycythemia Secondary to Tuberculosis of the Spleen. Report of a Case and Review of the Literature. WILLIAM J. FITZPATRICK AND STEVEN O. SCHWARTZ 660

Editorial: Immunological Aspects of BCG Vaccination. RENÉ J. DUBOS ... 670

Books 675

American Trudeau Society: Statement on BCG 681

Abstracts 65

NUMBER 6, DECEMBER, 1949

The Surgical Treatment of Recurrent and Chronic Spontaneous Pneumothorax of Nontuberculous Origin. RICHARD H. MEADE, JR., AND BRIAN B. BLADES 683

The Surgical Importance of the Anatomical Distribution of the Pulmonary Segments. EDWARD M. KENT 699

The Physiological Effects of Pneumoperitoneum upon the Respiratory Apparatus. GEORGE W. WRIGHT, RONALD PLACE, AND FRANK PRINCI 706

Evaluation of Streptomycin Regimens in the Treatment of Tuberculosis. An Account of the Study of the Veterans Administration, Army, and Navy, July 1946 to April 1949. WILLIAM B. TUCKER 715

Diffuse Pulmonary Granulomatosis in Young Women following Exposure to Beryllium Compounds in the Manufacture of Radio Tubes. Report of Five Cases. PAUL SLAVIN 755

Tuberculosis among Selective Service Registrants. MAPHEUS SMITH, LESTER T. REYNOLDS, AND M. ETHEL HAND 773

Case Reports:

Pulmonary Alveolar Adenomatosis. SIDNEY J. SHIPMAN, H. BRODIE STEPHENS, AND FREDERICK M. BINKLEY 788

Fatal Tension Pneumothorax Resulting from Diaphragmatic Rupture in a Patient Receiving Pneumoperitoneum. S. A. YANNITELLI, C. E. WOODRUFF, E. E. MUELLER, AND W. L. HOWARD 794

Tuberculous Arteritis of the Abdominal Aorta with Rupture into the Third Portion of the Duodenum. Report of a Case. HAROLD ZAROWITZ AND DAVID M. GRAYZEL 801

Letters to the Editors:

Chemotherapeutic Action of Streptomycin Para-aminosalicylate in Experimental Tuberculosis in Mice. GLADYS L. HOBBY, PETER P. REGNA, AND TULITA F. LENERT 808

The Effect of Antihistamine Medication on the Tuberculin Reaction. ALFRED R. HENDERSON 811

Obituary: BRUCE H. DOUGLAS, 1892–1949 812

Books 815

Index of Subjects and Authors 819

Index of Abstracts 81

RADIOGRAPHIC RULE of THREE

provides maximum

CLARITY

increased detail visibility . . .

CLARITY—a consequence of adequate detail, sharp definition, and desirable contrast—is easier to achieve when the three basic x-ray products bear the "Kodak" label. Made to work together, Kodak film, contact screens, and chemicals have qualities that complement each other . . . go a long way toward assuring the essential over-all radiographic clarity.

1 *Use*
KODAK FILM—
BLUE BRAND

OTHER KODAK PRODUCTS FOR RADIOGRAPHY

No-Screen Medical X-ray Film . . . Photoflure Films for photoradiography . . . Dental X-ray Films . . . Exposure Holders . . . Safelight Lamps and Filters . . . Identification Printer . . . Processing Hangers . . . Electric Chemical Mixers . . . Thermometers . . . Film Corner Cutter . . . Illuminators.

2 *Expose with*
KODAK SCREENS—
CONTACT (three types)

3 *Process with*
KODAK CHEMICALS
(liquid or powder)

EASTMAN KODAK COMPANY, ***Medical Division,*** **Rochester 4, N. Y.**

Kodak
TRADE-MARK

Bindings for Review Copies

THE AMERICAN REVIEW OF TUBERCULOSIS will bind current and back numbers of the REVIEW in standard uniform cloth binding.

Cost of binding, $3.00 per binding
Transportation and wrapping charges additional.

Please fill in the order below, detach this page and mail to:

AMERICAN REVIEW OF TUBERCULOSIS
1790 Broadway, New York 19, N. Y.

Please fill my order for binding my REVIEW volumes in the manner checked, supplying all the missing numbers.

☐ Original Articles and Abstracts of each volume separately at $6.00 per volume for binding.
☐ Articles and Abstracts for one volume in one binding at $3.00 per volume for binding.
☐ Articles and Abstracts for entire year bound separately at $3.00 per binding.

I desire volumes*.....bound and have sent to you at the above address under the date of.....by.....Volumes.....
(Pp. or Express)

NAME.....

ADDRESS.....

* If you order Volumes XI and XII bound and wish them combined, check here ☐

Industry, Tuberculosis Silicosis & Compensation

160 pages, clothbound, $2.00 postpaid

Edited by **Leroy U. Gardner, M.D.,** this useful volume assembles thirteen papers outlining significant developments in the handling of industrial X-ray surveys and follow-ups; in the identification and treatment of silicosis; in the field of workmen's compensation.

Recommended for thoughtful reading by industrial physicians, tuberculosis specialists, business and insurance executives.

Send your order today to the
National Tuberculosis Association
1790 Broadway New York 19, N. Y.

Present Concepts of Rehabilitation in Tuberculosis

by **NORMAN C. KIEFER, M.D.**

420 pages, cloth cover $3.50

In this new volume there is brought together, for the first time, an accurate summary of world research and achievement in every area of rehabilitation during the last decade.

More than 1,000 original papers are abstracted in this book, and in every case the salient features of each have been brought together in classified sections to provide a complete picture of approaches, procedures, and results.

A bibliography of more than 1,000 items supplies reference to basic sources, and a particularly comprehensive index facilitate the location of specific information.

Your order can be filled promptly.
NATIONAL TUBERCULOSIS ASSOCIATION
1790 Broadway, New York 19, N. Y.

Thirty-sixth Session:

TRUDEAU SCHOOL OF TUBERCULOSIS

AT SARANAC LAKE, N. Y.

In the Spring of 1950

Four Weeks Course Begins

MAY 1ST

Schedule of Instruction includes the history, etiology and epidemiology; pathology, bacteriology, physiology and biochemistry; clinics and bedside teaching, including surgical and special treatments; fungus infections; pneumoconioses; pulmonary tumors, and differential diagnosis of other lung disorders.

Clinical Facilities Available: Trudeau Sanatorium, Ray Brook State Hospital, Stony Wold Sanatorium, Will Rogers Memorial, Sanatorium Gabriels, V. A. Hospital at Sunmount, N. Y., and the General Hospital of Saranac Lake (chiefly surgical).

Research Facilities Available: Saranac Laboratory; Trudeau Laboratory; Physiology and Biochemistry Laboratories; Ray Brook State Hospital Laboratory, and the X-Ray Laboratories of Trudeau, Ray Brook and Stony Wold Sanatoria.

Lectures, Demonstrations and Conferences conducted by the Staffs and other experienced local clinicians. By invitation, recognized authorities give lectures on specific subjects.

Students Participate Actively in the study and discussion of cases.

Fee for Four Weeks Course is $100.00. The Trudeau School has been approved for training under Public Laws 16 and 346, for which arrangements should be made in advance. The class is limited, therefore early application is advised. A few scholarships are available.

For Schedule and other information write to
Secretary, TRUDEAU SCHOOL, Saranac Lake, N. Y.

Extending the *Usefulness* of Antibiotic Therapy in Tuberculosis

PARA-AMINOSALICYLIC ACID is a valuable synergist to streptomycin and dihydrostreptomycin therapy in tuberculosis. Its employment by oral administration along with injection of the antibiotics inhibits or significantly delays the emergence of resistant strains of organisms. The patient, therefore, may be given the benefit of a more prolonged period of effective chemotherapy.

Para-Aminosalicylic Acid by oral administration may be used as the sole chemotherapeutic agent when streptomycin or dihydrostreptomycin is contraindicated as, for example, in the presence of resistant organisms.

Para-Aminosalicylic Acid Merck, *a purified, white crystalline powder for oral administration, is available in 50 Gm. and 500 Gm. bottles and in 2.5 kilogram fiber drums. Literature on request.*

MERCK & CO., Inc.

MERCK

Manufacturing Chemists
RAHWAY, N. J.

Para-Aminosalicylic Acid Merck

[PAS]

ALUM ROCK SANATORIUM

SAN JOSE, CALIFORNIA

Telephone: CLayburn 8-4921

A non-profit sanatorium for the treatment of Tuberculosis and other diseases of the chest.

Medical Director
Buford H. Wardrip, M.D.
Associate Medical Director
C. G. Scarborough, M.D.

Visiting Medical Staff:

Harold Guyon Trimble, M.D., Oakland
Cabot Brown, M.D., San Francisco
J. Lloyd Eaton, M.D., Oakland
Ina Gourley, M.D., Oakland
Glenroy N. Pierce, M.D., San Francisco
Gerald L. Crenshaw, M.D., Oakland
James Robert Wood, M.D., Oakland

CHICAGO FRESH AIR HOSPITAL

A non-profit institution fully equipped for the care and management of diseases of the chest including treatments in the Emerson Lung Immobilizing Pressure Chamber.

Ideally located in a 20-acre park, accessible to bus, street car and elevated lines.

HUGO O. DEUSS, M.D., *Medical Director*
Telephone—Rogers Park 0321
2451 W. Howard Street at Western Ave. Chicago 45, Illinois

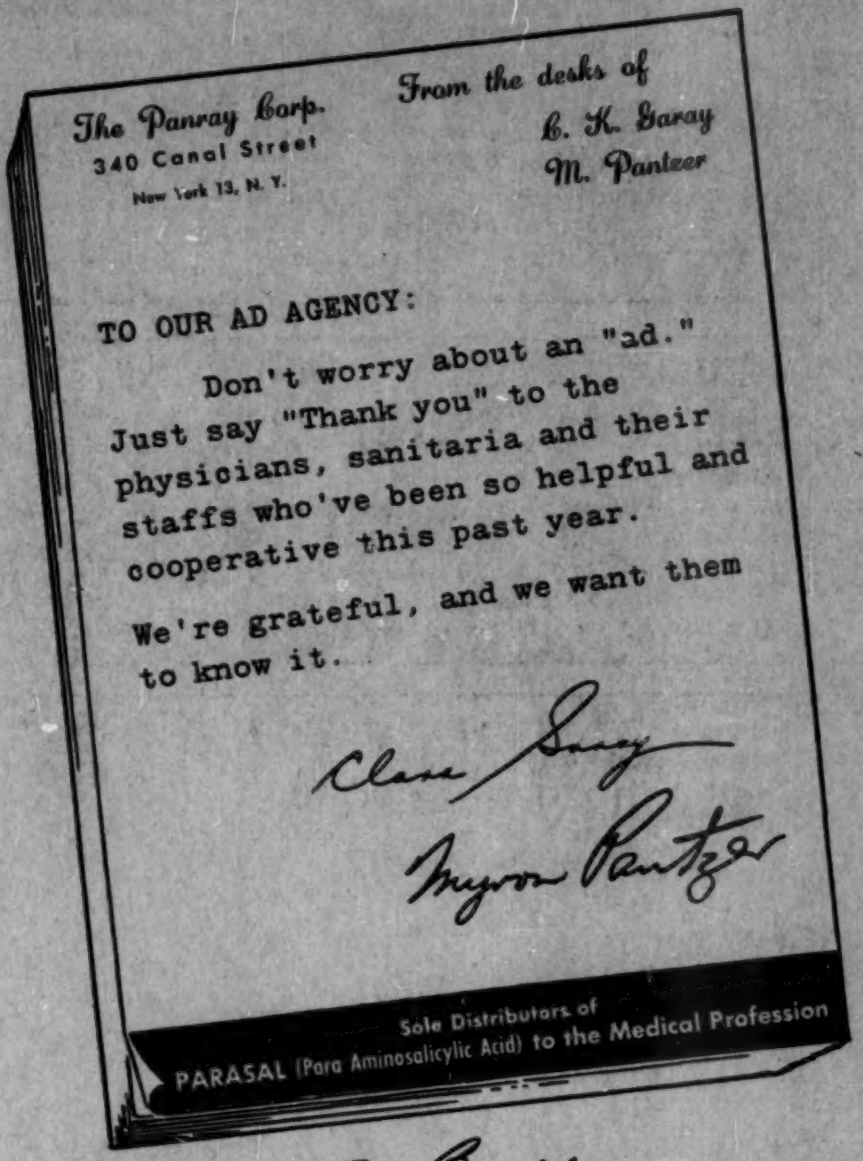
• *1949 Issues Needed* •

We will pay $1.00 per copy for any of the following issues, if they are in good condition. Mail them to the address below for prompt payment.

January, 1949
February, 1949
March, 1949

AMERICAN REVIEW OF TUBERCULOSIS

1790 Broadway, New York 19, New York


The Panray Corp.
340 Canal Street
New York 13, N. Y.
From the desks of
L. K. Garay
M. Pantzer
TO OUR AD AGENCY:
Don't worry about an "ad."
Just say "Thank you" to the physicians, sanitaria and their staffs who've been so helpful and cooperative this past year.
We're grateful, and we want them to know it.
Clare Garay
Myron Pantzer
Sole Distributors of
PARASAL (Para Aminosalicylic Acid) to the Medical Profession

~~AGENCY~~ NOTE: Besides "Season's Greetings," what more can we say?